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(54) Title: LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY

(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognosis or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

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TITLE OF THE INVENTION

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY,
MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS,
DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY

5 FIELD OF THE INVENTION

The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three loci mapping to chromosome 2, which show a linkage with epilepsy in patients. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA), to variations and mutations in these sequences and to the use thereof to assess, diagnose, prognosis or treat epilepsy. The invention also provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders.

BACKGROUND OF THE INVENTION

Epilepsy is one of the most common neurological conditions, occurring in about 1.0% of the general population. The disease is characterised by paroxysmal abnormal electrical discharges in the brain, which lead to transient cerebral dysfunction in the form of a seizure. A seizure is considered partial when the epileptic discharge is limited to part of one brain hemisphere, or generalised when it involves both cerebral hemispheres at the onset. The current classification of the epileptic syndromes rests on two criteria: 1) seizure type which may be generalised or partial at the onset, according to clinical and EEG features; and 2) etiology, which may be idiopathic, cryptogenic and symptomatic. Symptomatic epilepsies have multiple and heterogeneous causes including

brain injury, CNS infection, migrational and metabolic disorders. In the majority (65%) of the patients with either generalised or partial epilepsy, there is no underlying cause (idiopathic) or the cause is thought to be hidden or occult (cryptogenic). Also, in the idiopathic epileptic syndromes, there is no evidence of cerebral dysfunction other than the seizure, and the neurological examination is normal. There is now increasing evidence that in this latter group, genetic factors are important, especially for the idiopathic generalised epilepsy (IGE). In a recent study, Berkovic et al (1998) showed a 62% concordance rate in monozygotic twins overall for epilepsy. In this study, a higher concordance rate has been found in the generalised compared to the partial epilepsies, with 76% concordance rate for IGE. Recent studies using molecular genetic approaches have shown that many susceptibility genes for the epilepsies in human involve membrane ion channel and related proteins. These studies include the syndrome of benign familial neonatal convulsions where two loci have been identified [EBN1 on chromosome 20, the KCNQ2 gene (a potassium channel); and EBN2 on chromosome 8, the KCNQ3 gene (also a potassium channel)] (Bievert et al, 1998; Charlier et al, 1998; Singh et al, 1998), as well as autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE - chromosome 20, and the CHRNA4 gene (the neuronal nicotinic acetylcholine receptor alpha 4 subunit)] (Steinlein et al, 1995). More recently, there was a clinical description of a new syndrome (GEFS), which consisted of generalised epilepsy with febrile seizures. According to the current classification of epileptic syndrome, this syndrome would fall in the category of IGE, based on the seizure and electroencephalographic features. However, febrile seizures were present in all probands with GEFS, and the pattern of inheritance was clearly autosomal dominant, which are not part of the usual IGE phenotype. This unique GEFS syndrome has been shown to be associated with a mutation on the beta-1 subunit of brain voltage-gated sodium channel (SCN1B) gene (Wallace et

- al, 1998). In addition, three different groups, including the group of the present inventors, have identified another locus on chromosome 2 in large kindred with this specific syndrome (GEFS). This region contains many candidate genes, including a cluster of alpha subunits of sodium channels (SCNA). Voltage-gated sodium channels play an important role in the generation of action potential in nerve cells and muscle. The alpha subunit (SCNA) is the main component of the channel, and would be sufficient to generate an efficient channel when expressed in cells *in vitro*. In turn, the beta-1 and 2 subunits need an alpha subunit to give an effective channel.
- 5 The role of these subunits would be to modify the kinetic properties of the channel, mainly by fast inactivation of the sodium currents. The mutation found in the GEFS syndrome on the SCN1B gene was shown to reduce the fast inactivation of the sodium channels as compared to a normal SCNB1, when co-expressed with an alpha subunit. It is probable that this
- 10 could be the mechanism by which the mutation induce an hyperexcitability state in the brain, leading to seizure in humans. Interestingly, the mechanism of action of most of the anticonvulsant drugs is through a reduction of the repetitive firing of neurons, which is also known to be dependent on fast inactivation. These finding make it likely that additional
- 15 epilepsy genes will be identified by mutations in ion channels.
- 20

There thus remains a need to identify whether IGE is caused by a mutation in a sodium channel (SCNA). There also remains a need to assess whether a mutation(s) in SCNA is associated with GEFs. There also remains a need to determine whether a mutation that affects

25 the fast inactivation of a sodium channel, given the particular phenotype of GEFS or IGE, could be linked to a region which includes SCNA genes.

The present invention seeks to meet these and other needs.

The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

5 **SUMMARY OF THE INVENTION**

In one embodiment, the present invention relates to a genetic assay for determining predisposition to epilepsy.

10 In another embodiment, the present invention relates to a use of at least one of the loci of the present invention or an equivalent thereof (e.g. a loci in linkage disequilibrium therewith) as a marker for epilepsy and to determine the optimal treatment thereof (e.g. to guide the treatment modalities, thereby optimizing treatment to a particular clinical situation).

15 Yet in another embodiment, the present invention relates to an assay to screen for drugs for the treatment and/or prevention of epilepsy. In a particular embodiment, such assays can be designed using cells from patients having a known genotype at one of the loci of the present invention. These cells harboring recombinant vectors can enable an assessment of the functionality of the SCN1A, and/or SCN2A and/or
20 SCN3A and a combination thereof. Non-limiting examples of assays that could be used in accordance with the present invention include *cis-trans* assays similar to those described in U.S.P. 4,981,784.

25 It shall be understood that the determination of allelic variations in at least one of the loci of the present invention can be combined to the determination of allelic variation in other gene/markers linked to a predisposition to epilepsy. This combination of genotype analyses could lead to better diagnosis programs and/or treatment of epilepsy. Non-limiting examples of such markers include SCN1B, EBN1, KCNQ2, EBN2, KCNQ3, ADNFLE and CHRNA4.

In accordance with the present invention, there is therefore provided a method of determining an individual's predisposition to epilepsy, which comprises determining the genotype of at least one locus selected from the group consisting of SCN1A, SCN2A and SCN3A.

- 5 In one particular embodiment, the present invention provides a method of determining an individual's predisposition to epilepsy, which comprises determining a polymorphism (directly or indirectly by linkage disequilibrium) in a biological sample of an individual and analyzing the allelic variation in at least one of the loci selected from SCN1A, SCN2A
10 and SCN3A, thereby determining an individual's predisposition to epilepsy.

- In accordance with the present invention, there is also provided a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological
15 disorders comprising providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the
20 biological activity is a compound with this therapeutic effect.

- Also provided within the present invention is a compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A
25 protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene, wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

SCN1A, SCN2A and SCN3A refers to genes and proteins for Sodium Channel, Neuronal Type I, Alpha Subunit isoforms, and are described at OMIM # 182389 (Online Mendelian Inheritance in Man). These genes are structurally distinct sodium channel alpha-subunit isoforms in brain, also known as brain types I, II and III, respectively. Gene, cDNA and protein sequences for the various isoforms are shown in SEQ ID NOS:1-98.

Numerous methods for determining a genotype are known and available to the skilled artisan. All these genotype determination methods are within the scope of the present invention. In a particular embodiment of a method of the present invention, the determination of the genotype comprises an amplification of a segment of one of the loci selected from the group consisting of SCN1A, SCN2A and SCN3A and in a particularly preferred embodiment, the amplification is carried out using polymerase chain reaction.

In a particular embodiment, a pair of primers is designed to specifically amplify a segment of one of the markers of the present invention. This pair of primers is preferably derived from a nucleic acid sequence of SCN1A, SCN2A or SCN3A or from sequences flanking these genes, to amplify a segment of SCN1A, SCN2A or SCN3A (or to amplify a segment of a loci in linkage disequilibrium with at least one of the loci of the present invention). While a number of primers are exemplified herein, other primer pairs can be designed, using the sequences of the SCN1A, SCN2A and SCN3A nucleic acids molecules described hereinbelow. The same would apply to primer pairs from loci in linkage disequilibrium with the markers of the present invention.

Restriction fragment length polymorphisms can be used to determine polymorphisms at the SCN1A, SCN2A and SCN3A loci (and equivalent loci).

While human SCN1A, SCN2A and SCN3A are preferred sequences (nucleic acid and proteins) in accordance with the present invention, the invention should not be so limited. Indeed, in view of the significant conservation of these genes throughout evolution, sequences from different species, and preferably mammalian species, could be used in the assays of the present invention. One non-limiting example is the rat SCN1A ortholog gene which shows 95% identity with the human SCN1A gene. The significant conservation of the mouse SCN1A gene can also be observed in OMIM (see above).

In order to provide a clear and consistent understanding of terms used in the present description, a number of definitions are provided hereinbelow.

As used herein the term "RFLP" refers to restriction fragment length polymorphism.

The terms "polymorphism", "DNA polymorphism" and the like, refer to any sequence in the human genome which exists in more than one version or variant in the population.

The term "linkage disequilibrium" refers to any degree of non-random genetic association between one or more allele(s) of two different polymorphic DNA sequences, that is due to the physical proximity of the two loci. Linkage disequilibrium is present when two DNA segments that are very close to each other on a given chromosome will tend to remain unseparated for several generations with the consequence that alleles of a DNA polymorphism (or marker) in one segment will show a non-random association with the alleles of a different DNA polymorphism (or marker) located in the other DNA segment nearby. Hence, testing of a marker in linkage disequilibrium with the polymorphisms of the present invention at the SCN1A, SCN2A and/or SCN3A genes (indirect testing), will give almost the same information as

testing for the SCN1A, SCN2A and SCN3A polymorphisms directly. This situation is encountered throughout the human genome when two DNA polymorphisms that are very close to each other are studied. Linkage disequilibriums are well known in the art and various degrees of linkage
5 disequilibrium can be encountered between two genetic markers so that some are more closely associated than others.

It shall be recognized by the person skilled in the art to which the present invention pertains, that since some of the polymorphisms or mutations herein identified in the SCN1A, SCN2A
10 and/or SCN3A genes can be within the coding region of the genes and therefore expressed, that the present invention should not be limited to the identification of the polymorphisms/mutations at the DNA level (whether on genomic DNA, amplified DNA, cDNA, or the like). Indeed, the herein-identified polymorphisms and/or mutations could be detected at
15 the mRNA or protein level. Such detections of polymorphism identification on mRNA or protein are known in the art. Non-limiting examples include detection based on oligos designed to hybridize to mRNA or ligands such as antibodies which are specific to the encoded polymorphism (i.e. specific to the protein fragment encoded by the distinct polymorphisms).

20 Nucleotide sequences are presented herein by single strand, in the 5' to 3' direction, from left to right, using the one letter nucleotide symbols as commonly used in the art and in accordance with the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission.

25 Unless defined otherwise, the scientific and technological terms and nomenclature used herein have the same meaning as commonly understood by a person of ordinary skill to which this invention pertains. Generally, the procedures for cell cultures, infection, molecular biology methods and the like are common methods

used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook et al. (1989, Molecular Cloning-A Laboratory Manual, Cold Spring Harbor Laboratories) and Ausubel et al. (1994, Current Protocols in Molecular Biology, Wiley, New York).

5 The present description refers to a number of routinely used recombinant DNA (rDNA) technology terms. Nevertheless, definitions of selected examples of such rDNA terms are provided for clarity and consistency.

10 As used herein, "nucleic acid molecule", refers to a polymer of nucleotides. Non-limiting examples thereof include DNA (i.e. genomic DNA, cDNA, RNA molecules (i.e. mRNA) and chimeras of DNA and RNA. The nucleic acid molecule can be obtained by cloning techniques or synthesized. DNA can be double-stranded or single-stranded (coding strand or non-coding strand [antisense]).

15 The term "recombinant DNA" as known in the art refers to a DNA molecule resulting from the joining of DNA segments. This is often referred to as genetic engineering.

20 The term "DNA segment", is used herein, to refer to a DNA molecule comprising a linear stretch or sequence of nucleotides. This sequence when read in accordance with the genetic code, can encode a linear stretch or sequence of amino acids which can be referred to as a polypeptide, protein, protein fragment and the like.

25 The terminology "amplification pair" refers herein to a pair of oligonucleotides (oligos) of the present invention, which are selected to be used together in amplifying a selected nucleic acid sequence by one of a number of types of amplification processes, preferably a polymerase chain reaction. Other types of amplification processes include ligase chain reaction, strand displacement amplification, or nucleic acid sequence-based amplification, as explained

in greater detail below. As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions.

The nucleic acid (i.e. DNA, RNA or chimeras thereof)
5 for practicing the present invention may be obtained according to well known methods.

Oligonucleotide probes or primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted genomes employed.
10 In general, the oligonucleotide probes or primers are at least 12 nucleotides in length, preferably between 15 and 24 molecules, and they may be adapted to be especially suited to a chosen nucleic acid amplification system. As commonly known in the art, the oligonucleotide probes and primers can be designed by taking into consideration the
15 melting point of hybridization thereof with its targeted sequence (see below and in Sambrook et al., 1989, Molecular Cloning -A Laboratory Manual, 2nd Edition, CSH Laboratories; Ausubel et al., 1989, in Current Protocols in Molecular Biology, John Wiley & Sons Inc., N.Y.).

The term "DNA" molecule or sequence (as well as
20 sometimes the term "oligonucleotide") refers to a molecule comprised of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). Sometimes, in a double-stranded form, it can comprise or include a "regulatory element" according to the present invention, as the term is defined herein. The term "oligonucleotide" or "DNA" can be found
25 in linear DNA molecules or fragments, viruses, plasmids, vectors, chromosomes or synthetically derived DNA. As used herein, particular double-stranded DNA sequences may be described according to the normal convention of giving only the sequence in the 5' to 3' direction. Of

course, as very well-known, DNA molecules or sequences are often in single stranded form.

“Nucleic acid hybridization” refers generally to the hybridization of two single-stranded nucleic acid molecules having complementary base sequences, which under appropriate conditions will form a thermodynamically favored double-stranded structure. Examples of hybridization conditions can be found in the two laboratory manuals referred to above (Sambrook et al., 1989, *supra* and Ausubel et al., 1989, *supra*) and are commonly known in the art. In the case of a hybridization to a nitrocellulose filter, as for example in the well known Southern blotting procedure, a nitrocellulose filter can be incubated overnight at 65°C with a labeled probe in a solution containing 50% formamide, high salt (5 x SSC or 5 x SSPE), 5 x Denhardt's solution, 1% SDS, and 100 µg/ml denatured carrier DNA (i.e. salmon sperm DNA). The non-specifically binding probe can then be washed off the filter by several washes in 0.2 x SSC/0.1% SDS at a temperature which is selected in view of the desired stringency: room temperature (low stringency), 42°C (moderate stringency) or 65°C (high stringency). The selected temperature is based on the melting temperature (T_m) of the DNA hybrid. Of course, RNA-DNA hybrids can also be formed and detected. In such cases, the conditions of hybridization and washing can be adapted according to well known methods by the person of ordinary skill. Stringent conditions will be preferably used (Sambrook et al., 1989, *supra*).

Probes of the invention can be utilized with naturally occurring sugar-phosphate backbones as well as modified backbones including phosphorothioates, dithionates, alkyl phosphonates and α -nucleotides and the like. Modified sugar-phosphate backbones are generally taught by Miller, 1988, Ann. Reports Med. Chem. 23:295 and Moran et al., 1987, Nucleic Acids Res., 14:5019. Probes of the invention

can be constructed of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), and preferably of DNA.

The types of detection methods in which probes can be used include Southern blots (DNA detection), dot or slot blots (DNA, RNA), and Northern blots (RNA detection). Although less preferred, labeled proteins could also be used to detect a particular nucleic acid sequence to which it binds. More recently, PNAs have been described (Nielsen et al. 1999, Current Opin. Biotechnol. 10:71-75). PNAs could also be used to detect the polymorphisms of the present invention. Other detection methods include kits containing probes on a dipstick setup and the like.

Although the present invention is not specifically dependent on the use of a label for the detection of a particular nucleic acid sequence, such a label might be beneficial, by increasing the sensitivity of the detection. Furthermore, it enables automation. Probes can be labeled according to numerous well known methods (Sambrook et al., 1989, supra). Non-limiting examples of labels include ^3H , ^{14}C , ^{32}P , and ^{35}S . Non-limiting examples of detectable markers include ligands, fluorophores, chemiluminescent agents, enzymes, and antibodies. Other detectable markers for use with probes, which can enable an increase in sensitivity of the method of the invention, include biotin and radionucleotides. It will become evident to the person of ordinary skill that the choice of a particular label dictates the manner in which it is bound to the probe.

As commonly known, radioactive nucleotides can be incorporated into probes of the invention by several methods. Non-limiting examples thereof include kinasing the 5' ends of the probes using gamma ^{32}P ATP and polynucleotide kinase, using the Klenow fragment of Pol I of *E. coli* in the presence of radioactive dNTP (i.e. uniformly labeled DNA

probe using random oligonucleotide primers in low-melt gels), using the SP6/T7 system to transcribe a DNA segment in the presence of one or more radioactive NTP, and the like.

As used herein, "oligonucleotides" or "oligos" define a molecule having two or more nucleotides (ribo or deoxyribonucleotides). The size of the oligo will be dictated by the particular situation and ultimately on the particular use thereof and adapted accordingly by the person of ordinary skill. An oligonucleotide can be synthesised chemically or derived by cloning according to well known methods.

As used herein, a "primer" defines an oligonucleotide which is capable of annealing to a target sequence, thereby creating a double stranded region which can serve as an initiation point for nucleic acid synthesis under suitable conditions.

Amplification of a selected, or target, nucleic acid sequence may be carried out by a number of suitable methods. See generally Kwoh et al., 1990, Am. Biotechnol. Lab. 8:14-25. Numerous amplification techniques have been described and can be readily adapted to suit particular needs of a person of ordinary skill. Non-limiting examples of amplification techniques include polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), transcription-based amplification, the Q-beta replicase system and NASBA (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 1989, *supra*). Preferably, amplification will be carried out using PCR.

Polymerase chain reaction (PCR) is carried out in accordance with known techniques. See, e.g., U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; and 4,965,188 (the disclosures of all three U.S. Patent are incorporated herein by reference). In general, PCR involves, a

treatment of a nucleic acid sample (e.g., in the presence of a heat stable DNA polymerase) under hybridizing conditions, with one oligonucleotide primer for each strand of the specific sequence to be detected. An extension product of each primer which is synthesized is complementary to each of the two nucleic acid strands, with the primers sufficiently complementary to each strand of the specific sequence to hybridize therewith. The extension product synthesized from each primer can also serve as a template for further synthesis of extension products using the same primers. Following a sufficient number of rounds of synthesis of extension products, the sample is analysed to assess whether the sequence or sequences to be detected are present. Detection of the amplified sequence may be carried out by visualization following EtBr staining of the DNA following gel electrophoresis, or using a detectable label in accordance with known techniques, and the like. For a review on PCR techniques (see PCR Protocols, A Guide to Methods and Amplifications, Michael et al. Eds, Acad. Press, 1990).

Ligase chain reaction (LCR) is carried out in accordance with known techniques (Weiss, 1991, Science 254:1292). Adaptation of the protocol to meet the desired needs can be carried out by a person of ordinary skill. Strand displacement amplification (SDA) is also carried out in accordance with known techniques or adaptations thereof to meet the particular needs (Walker et al., 1992, Proc. Natl. Acad. Sci. USA 89:392-396; and *ibid.*, 1992, Nucleic Acids Res. 20:1691-1696).

As used herein, the term "gene" is well known in the art and relates to a nucleic acid sequence defining a single protein or polypeptide. A "structural gene" defines a DNA sequence which is transcribed into RNA and translated into a protein having a specific amino acid sequence thereby giving rise to a specific polypeptide or protein. It will be readily recognized by the person of ordinary skill, that the nucleic

acid sequence of the present invention can be incorporated into anyone of numerous established kit formats which are well known in the art.

A "heterologous" (i.e. a heterologous gene) region of a DNA molecule is a subsegment of DNA within a larger segment that is not
5 found in association therewith in nature. The term "heterologous" can be similarly used to define two polypeptidic segments not joined together in nature. Non-limiting examples of heterologous genes include reporter genes such as luciferase, chloramphenicol acetyl transferase, beta-galactosidase, and the like which can be juxtaposed or joined to
10 heterologous control regions or to heterologous polypeptides.

The term "vector" is commonly known in the art and defines a plasmid DNA, phage DNA, viral DNA and the like, which can serve as a DNA vehicle into which DNA of the present invention can be cloned. Numerous types of vectors exist and are well known in the art.

15 The term "expression" defines the process by which a gene is transcribed into mRNA (transcription), the mRNA is then being translated (translation) into one polypeptide (or protein) or more.

The terminology "expression vector" defines a vector or vehicle as described above but designed to enable the expression of an
20 inserted sequence following transformation into a host. The cloned gene (inserted sequence) is usually placed under the control of control element sequences such as promoter sequences. The placing of a cloned gene under such control sequences is often referred to as being operably linked to control elements or sequences.

25 Operably linked sequences may also include two segments that are transcribed onto the same RNA transcript. Thus, two sequences, such as a promoter and a "reporter sequence" are operably linked if transcription commencing in the promoter will produce an RNA transcript of the reporter sequence. In order to be "operably linked" it is

not necessary that two sequences be immediately adjacent to one another.

Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a
5 prokaryotic or eukaryotic host or both (shuttle vectors) and can additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

Prokaryotic expressions are useful for the preparation
10 of large quantities of the protein encoded by the DNA sequence of interest. This protein can be purified according to standard protocols that take advantage of the intrinsic properties thereof, such as size and charge (i.e. SDS gel electrophoresis, gel filtration, centrifugation, ion exchange chromatography...). In addition, the protein of interest can be purified via
15 affinity chromatography using polyclonal or monoclonal antibodies. The purified protein can be used for therapeutic applications.

The DNA construct can be a vector comprising a promoter that is operably linked to an oligonucleotide sequence of the present invention, which is in turn, operably linked to a heterologous gene,
20 such as the gene for the luciferase reporter molecule. "Promoter" refers to a DNA regulatory region capable of binding directly or indirectly to RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of the present invention, the promoter is bound at its 3' terminus by the transcription initiation site and
25 extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter will be found a transcription initiation site (conveniently defined by mapping with S1 nuclease), as well as protein binding domains (consensus sequences) responsible for the

binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain "TATA" boxes and "CCAT" boxes. Prokaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

5 In accordance with one embodiment of the present invention, an expression vector can be constructed to assess the functionality of specific alleles of the SCN1A, SCN2A and SCN3A sodium channels. Non-limiting examples of such expression vectors include a vector comprising the nucleic acid sequence encoding one of the sodium
10 channels (or part thereof) according to the present invention. These vectors can be transfected in cells. The sequences of the alpha subunit of the sodium channels in accordance with the present invention and their structure-function relationship could be assessed by a number of methods known to the skilled artisan. One non-limiting example includes the use of
15 cells expressing the β -1 and β -2 subunits and the sequence of an alpha subunit in accordance with the present invention. For example, an alpha subunit having a mutation, which is linked to epilepsy, could be compared to a sequence devoid of that mutation, as a control. In such cells, the functionality of the sodium channel could be tested as known to the skilled
20 artisan and these cells could be used to screen for agents which could modulate the activity of the sodium channel. For example, agents could be tested and selected, which would reduce the hyperexcitability state of the sodium channel (e.g. their reduction in fast inactivation). Agents known to the person of ordinary skill as affecting other sodium channels
25 could be tested, for example, separately or in batches. Of course, it will be understood that the SCN1A, SCN2A and/or SCN3A genes expressed by these cells can be modified at will (e.g. by *in vitro* mutagenesis or the like).

As used herein, the designation "functional derivative" denotes, in the context of a functional derivative of a sequence whether a

nucleic acid or amino acid sequence, a molecule that retains a biological activity (either function or structural; e.g. sodium channel function or structure) that is substantially similar to that of the original sequence. This functional derivative or equivalent may be a natural derivative or may be prepared synthetically. Such derivatives include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, provided that the biological activity of the protein is conserved. The same applies to derivatives of nucleic acid sequences which can have substitutions, deletions, or additions of one or more nucleotides, provided that the biological activity of the sequence is generally maintained. When relating to a protein sequence, the substituting amino acid generally has chemico-physical properties which are similar to that of the substituted amino acid. The similar chemico-physical properties include, similarities in charge, bulkiness, hydrophobicity, hydrophylicity and the like. The term "functional derivatives" is intended to include "fragments", "segments", "variants", "analogs" or "chemical derivatives" of the subject matter of the present invention. The genetic code, the chemico-physical characteristics of amino acids and teachings relating to conservative vs. non-conservative mutations are well-known in the art. Non-limiting examples of textbooks teaching such information are Stryer, Biochemistry, 3rd ed.; and Lehninger, Biochemistry, 3rd ed. The functional derivatives of the present invention can be synthesized chemically or produced through recombinant DNA technology. all these methods are well known in the art.

The term "variant" refers herein to a protein or nucleic acid molecule which is substantially similar in structure and biological activity to the protein or nucleic acid of the present invention.

As used herein, "chemical derivatives" is meant to cover additional chemical moieties not normally part of the subject matter of the invention. Such moieties could affect the physico-chemical

characteristic of the derivative (i.e. solubility, absorption, half life, decrease of toxicity and the like). Such moieties are exemplified in Remington's Pharmaceutical Sciences (1980). Methods of coupling these chemical-physical moieties to a polypeptide or nucleic acid sequence are well known in the art.

The term "allele" defines an alternative form of a gene which occupies a given locus on a chromosome.

As commonly known, a "mutation" is a detectable change in the genetic material which can be transmitted to a daughter cell. As well known, a mutation can be, for example, a detectable change in one or more deoxyribonucleotide. For example, nucleotides can be added, deleted, substituted for, inverted, or transposed to a new position. Spontaneous mutations and experimentally induced mutations exist. The result of a mutations of nucleic acid molecule is a mutant nucleic acid molecule. A mutant polypeptide can be encoded from this mutant nucleic acid molecule.

As used herein, the term "purified" refers to a molecule having been separated from a cellular component. Thus, for example, a "purified protein" has been purified to a level not found in nature. A "substantially pure" molecule is a molecule that is lacking in all other cellular components.

As used herein, "SCNA biological activity" refers to any detectable biological activity of SCN1A, SCN2A or SCN3A gene or protein (herein sometimes collectively called SCNA genes or SCNA proteins). This includes any physiological function attributable to an SCNA gene or protein. It can include the specific biological activity of SCNA proteins which is efflux of sodium or related ions. This includes measurement of channel properties such as, but not limited to: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels, 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. At a larger scale, SCNA biological activity includes transmission of impulses through cells, wherein changes in transmission characteristics caused by modulators of SCNA proteins can be identified. Non-limiting examples of such measurements of these biological activities may be made directly or indirectly, such as through the transient accumulation of ions in a cell, dynamics of membrane depolarization, etc. SCNA biological activity is not limited, however, to these most important biological activities herein identified. Biological activities may also include simple binding or pKa analysis of SCNA with compounds, substrates, interacting proteins, and the like. For example, by measuring the effect of a test compound on its ability to increase or inhibit such SCNA binding or interaction is measuring a biological activity of SCNA according to this invention. SCNA biological activity includes any standard biochemical measurement of SCNA such as conformational changes, phosphorylation status or any other feature of the protein that can be measured with techniques known in the art. Finally, SCNA biological activity also includes activities related to SCNA gene transcription or translation, or any biological activities of such transcripts or translation products.

As used herein, the terms "molecule", "compound", "agent" or "ligand" are used interchangeably and broadly to refer to natural, synthetic or semi-synthetic molecules or compounds. The term "molecule" therefore denotes for example chemicals, macromolecules, cell or tissue extracts (from plants or animals) and the like. Non limiting examples of molecules include nucleic acid molecules, peptides, ligands (including, for example, antibodies and carbohydrates) and pharmaceutical agents. The agents can be selected and screened by a

variety of means including random screening, rational selection and by rational design using for example protein or ligand modelling methods such as computer modelling. The terms "rationally selected" or "rationally designed" are meant to define compounds which have been chosen
5 based on the configuration of the interacting domains of the present invention. As will be understood by the person of ordinary skill, macromolecules having non-naturally occurring modifications are also within the scope of the term "molecule". For example, peptidomimetics, well known in the pharmaceutical industry and generally referred to as
10 peptide analogs can be generated by modelling as mentioned above. Similarly, in a preferred embodiment, the polypeptides of the present invention are modified to enhance their stability. It should be understood that in most cases this modification should not alter the biological activity of the protein. The molecules identified in accordance with the teachings
15 of the present invention have a therapeutic value in diseases or conditions in which sodium transport through the sodium channels is compromised by a mutation (or combination thereof) in one of the genes identified in accordance with the present invention. Alternatively, the molecules identified in accordance with the teachings of the present invention find
20 utility in the development of compounds which can modulate the activity of the alpha subunit sodium channels and/or the action potential in nerve cells and muscles cells (e.g. restore the fast inactivation of the sodium channel to normal levels).

As used herein, agonists and antagonists also include
25 potentiators of known compounds with such agonist or antagonist properties. In one embodiment, modulators of the fast inactivation of the sodium channel in accordance with the present invention can be identified and selected by contacting the indicator cell with a compound or mixture or library of molecules for a fixed period of time.

As used herein the recitation "indicator cells" refers to cells that express at least one sodium channel α subunit (SCNA) according to the present invention. As alluded to above, such indicator cells can be used in the screening assays of the present invention. In
5 certain embodiments, the indicator cells have been engineered so as to express a chosen derivative, fragment, homolog, or mutant of the combination of genotypes of the present invention. The cells can be yeast cells or higher eukaryotic cells such as mammalian cells. In one particular embodiment, the indicator cell would be a yeast cell harboring vectors
10 enabling the use of the two hybrid system technology, as well known in the art (Ausubel et al., 1994, *supra*) and can be used to test a compound or a library thereof. In another embodiment, the *cis-trans* assay as described in USP 4,981,784, can be adapted and used in accordance with the present invention. Such an indicator cell could be used to rapidly
15 screen at high-throughput a vast array of test molecules. In a particular embodiment, the reporter gene is luciferase or beta-Gal.

It shall be understood that the "*in vivo*" experimental model can also be used to carry out an "*in vitro*" assay. For example, cellular extracts from the indicator cells can be prepared and used in an
20 "*in vitro*" test. A non-limiting example thereof include binding assays.

In some embodiments, it might be beneficial to express a fusion protein. The design of constructs therefor and the expression and production of fusion proteins and are well known in the art (Sambrook et al., 1989, *supra*; and Ausubel et al., 1994, *supra*).

25 Non-limiting examples of such fusion proteins include hemagglutinin fusions and Gluthione-S-transferase (GST) fusions and Maltose binding protein (MBP) fusions. In certain embodiments, it might be beneficial to introduce a protease cleavage site between the two polypeptide sequences which have been fused. Such protease cleavage

sites between two heterologously fused polypeptides are well known in the art.

In certain embodiments, it might also be beneficial to fuse the protein of the present invention to signal peptide sequences enabling a secretion of the fusion protein from the host cell. Signal peptides from diverse organisms are well known in the art. Bacterial OmpA and yeast Suc2 are two non-limiting examples of proteins containing signal sequences. In certain embodiments, it might also be beneficial to introduce a linker (commonly known) between the interaction domain and the heterologous polypeptide portion. Such fusion protein find utility in the assays of the present invention as well as for purification purposes, detection purposes and the like.

For certainty, the sequences and polypeptides useful to practice the invention include without being limited thereto mutants, homologs, subtypes, alleles and the like. It shall be understood that generally, the sequences of the present invention should encode a functional (albeit defective) alpha subunit of sodium channels (SCNA). It will be clear to the person of ordinary skill that whether the SCNA sequence of the present invention, variant, derivative, or fragment thereof retains its function, can be determined by using the teachings and assays of the present invention and the general teachings of the art.

It should be understood that the SCNA protein of the present invention can be modified, for example by *in vitro* mutagenesis, to dissect the structure-function relationship thereof and permit a better design and identification of modulating compounds. However, some derivative or analogs having lost their biological function may still find utility, for example for raising antibodies. These antibodies could be used for detection or purification purposes. In addition, these antibodies could

also act as competitive or non-competitive inhibitor and be found to be modulators of the activity of the SCNA proteins of the present invention.

A host cell or indicator cell has been "transfected" by exogenous or heterologous DNA (e.g. a DNA construct) when such DNA
5 has been introduced inside the cell. The transfecting DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transfecting DNA may be maintained on a episomal element such as a plasmid. With respect to eukaryotic cells, a stably transfected
10 cell is one in which the transfecting DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transfecting DNA. Transfection methods are well
15 known in the art (Sambrook et al., 1989, *supra*; Ausubel et al., 1994 *supra*). The use of a mammalian cell as indicator can provide the advantage of furnishing an intermediate factor, which permits for example the interaction of two polypeptides which are tested, that might not be present in lower eukaryotes or prokaryotes. It will be understood that
20 extracts from mammalian cells for example could be used in certain embodiments, to compensate for the lack of certain factors.

In general, techniques for preparing antibodies (including monoclonal antibodies and hybridomas) and for detecting antigens using antibodies are well known in the art (Campbell, 1984, In
25 "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", Elsevier Science Publisher, Amsterdam, The Netherlands) and in Harlow et al., 1988 (in: Antibody-A Laboratory Manual, CSH Laboratories). The present invention also provides polyclonal, monoclonal antibodies, or humanized versions

thereof, chimeric antibodies and the like which inhibit or neutralize their respective interaction domains and/or are specific thereto.

From the specification and appended claims, the term therapeutic agent should be taken in a broad sense so as to also include
5 a combination of at least two such therapeutic agents. Further, the DNA segments or proteins according to the present invention could be introduced into individuals in a number of ways. For example, cells can be isolated from the afflicted individual, transformed with a DNA construct according to the invention and reintroduced to the afflicted individual in a
10 number of ways. Alternatively, the DNA construct can be administered directly to the afflicted individual. The DNA construct can also be delivered through a vehicle such as a liposome, which can be designed to be targeted to a specific cell type, and engineered to be administered through different routes.

15 For administration to humans, the prescribing medical professional will ultimately determine the appropriate form and dosage for a given patient, and this can be expected to vary according to the chosen therapeutic regimen (i.e. DNA construct, protein, cells), the response and condition of the patient as well as the severity of the disease.

20 Composition within the scope of the present invention should contain the active agent (i.e. molecule, hormone) in an amount effective to achieve the desired therapeutic effect while avoiding adverse side effects. Typically, the nucleic acids in accordance with the present invention can be administered to mammals (i.e. humans) in doses ranging
25 from 0.005 to 1 mg per kg of body weight per day of the mammal which is treated. Pharmaceutically acceptable preparations and salts of the active agent are within the scope of the present invention and are well known in the art (Remington's Pharmaceutical Science, 16th Ed., Mack Ed.). For the administration of polypeptides, antagonists, agonists and the like, the

amount administered should be chosen so as to avoid adverse side effects. The dosage will be adapted by the clinician in accordance with conventional factors such as the extent of the disease and different parameters from the patient. Typically, 0.001 to 50 mg/kg/day will be
5 administered to the mammal.

The present invention also relates to a kit for diagnosing and/or prognosing epilepsy, and/or predicting response to a medication comprising an assessment of a genotype at SCNA loci of the present invention (or loci in linkage disequilibrium therewith) using a
10 nucleic acid fragment, a protein or a ligand, a restriction enzyme or the like, in accordance with the present invention. For example, a compartmentalized kit in accordance with the present invention includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of
15 plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include in one particular
20 embodiment a container which will accept the test sample (DNA protein or cells), a container which contains the primers used in the assay, containers which contain enzymes, containers which contain wash reagents, and containers which contain the reagents used to detect the extension products.

25 **BRIEF DESCRIPTION OF THE DRAWINGS**

Having thus generally described the invention, reference will now be made to the accompanying drawings, showing by way of illustration a preferred embodiment thereof, and in which:

Figure 1 shows the IGE candidate region on ch 2q23-q31. Order and distance between markers are according to Gyapay et al., 1994.

Figure 2 shows the PCR primers used for genomic
5 PCR-SSCP of SCN1A;

Figure 3 shows the sequence of the SCN1A mutations found in epilepsy patients;

Figure 4 shows the PCR primers used for genomic
PCR-SSCP of SCN2A;

10 Figure 5 shows the mutation found in epilepsy patients in SCN2A;

Figure 6 shows the PCR primers used for genomic
PCR-SSCP of SCN3A; and

15 Figure 7 shows the mutation found in epilepsy patients in SCN3A.

Sequences are also shown in the Sequence Listing. For example, SEQ ID NO.:1 shows the nucleic acid sequence of the adult form of SCN1A; SEQ ID NO.:2 shows the nucleic acid sequence of the neonatal form of SCN1A; SEQ ID NO.:3 shows the protein sequence of the adult form of SCN1A; SEQ ID NO.:4 shows the protein sequence of the neonatal form of SCN1A; SEQ ID NOS.:5-32 show the genomic
20 sequence of SCN1A; SEQ ID NO.:33 shows the cDNA sequence of the adult form of SCN2A; SEQ ID NO.:34 shows the cDNA sequence of the neonatal form of SCN2A; SEQ ID NO.:35 shows the protein sequence of the adult form of SCN2A; SEQ ID NO.:36 shows the protein sequence of the neonatal form of SCN2A; SEQ ID NOS.:37-64 show the genomic
25 sequence of SCN2A; SEQ ID NO.:65 shows the cDNA sequence of the adult form of SCN3A; SEQ ID NO.:66 shows the cDNA sequence of the neonatal form of SCN3A; SEQ ID NO.:67 shows the protein sequence of

the adult form of SCN3A; SEQ ID NO.:68 shows the protein sequence of the neonatal form of SCN3A; and SEQ ID NOS.:69-98 show the genomic sequence of SCN3A. Rat SCNA1 sequences can be found in GenBank under accession numbers M22253 and X03638.

5 Other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawing which is exemplary and should not be interpreted as limiting the scope of the present invention.

10 **DESCRIPTION OF THE PREFERRED EMBODIMENT**

Epilepsy is one of the most common neurological conditions, affecting 1-2% of the general population. Familial aggregation studies have shown an increased risk for epilepsy in relatives of probands with different types of epilepsy, and especially for the idiopathic
15 generalized epilepsies (IGEs). The epilepsy genes identified to date account for a very small proportion of all the epilepsies. In addition, they have been identified in rare syndromes where the pattern of inheritance was clearly Mendelian. This is not the case for the vast majority of epileptic patients, however, where the pattern of inheritance is not
20 compatible with a simple Mendelian model. In fact, most authors consider epilepsy to be the result of a combination of many different genetic and environmental factors, features of a complex trait. While the pattern of inheritance is not mendelian, sporadic IGE cases may be caused by specific mutations in the same genes. Based on this assumption, a large
25 cohort of IGE patients was tested for mutation in the SCNA genes.

In order to localize the gene causing epilepsy in a large family segregating an autosomal dominant form of IGE, 41 family members, including 21 affected individuals, were genotyped. A detailed clinical description of this family has been reported elsewhere (Scheffer

and Berkovic 1997). The majority of patients in this family present a benign epilepsy syndrome occurring in childhood and characterized by frequent generalized tonic-clonic seizures not always associated with fever: a syndrome called febrile seizures plus (FS+). However, several
5 patients presented other types of generalized seizures (GTCS) as well, such as myoclonic seizures and absences (Scheffer and Berkovic 1997). Mean age at onset was 2.2 years and offset was 11.7 years. Neurological examination and intellect were normal in all individuals except one, who had moderate intellectual disability. EEG recordings were normal in most
10 patients. However, in three individuals generalized epileptiform activity was found and four patients had mild or moderate diffuse background slowing. Table 1 shows the different types of seizures found in the 21 patients included in this study.

Table 1. Different types of generalized seizures found in the 21 patients included in the linkage analysis.

Type of seizures	n
Febrile convulsions alone	9
GTCSs ^a + absence seizures	4
GTCSs + myoclonic seizures	1
GTCSs + atonic seizures	1
Solitary afebril GTCS	1
Secondary epilepsy + mental retardation	1
Unwitnessed events	4

^a GTCS: generalized tonic clonic seizure

5

A genome wide search examining 190 markers identified linkage of IGE to chromosome (ch) 2 based on an initial positive lod score for marker D2S294 ($Z=4.4$, $(=0)$). A total of 24 markers were tested on ch 2q in order to define the smallest IGE candidate region. Table 2 shows the two-point lod scores for 17 markers spanning the IGE candidate region. The highest lod score ($Z_{\max}=5.29$; $(=0)$) was obtained with marker D2S324. Critical recombination events mapped the IGE gene to a 29cM region flanked by markers D2S156 and D2S311, assigning the IGE locus to ch 2q23-q31 (Figure 1). Although the relationship of FS+ with other IGE phenotypes remains unclear, the observation that in this family, several affected individuals have different types of generalized seizures, suggests that seizure predisposition determined by the ch 2q-IGE gene could be modified by other genes and/or environmental factors, to produce different seizure types.

Table 2. Two-point lod-scores for 17 markers localized
on ch 2q23-q31.

Locus	Recombination fractions							Zmax	max
	0	0.05	0.1	0.15	0.2	0.3	0.4		
D2S142	0.99	1.94	1.97	1.85	1.68	1.22	0.66	1.98	0.078
D2S284	1.3	1.18	1.06	0.94	0.82	0.57	0.3	1.3	0
D2S306	1.9	2.82	2.74	2.52	2.25	1.6	0.85	2.82	0.057
D2S156	2.15	3.05	2.96	2.73	2.43	1.73	0.93	3.05	0.056
D2S354	4.72	4.26	3.82	3.4	2.97	2.1	1.13	4.72	0
D2S111	5.15	4.71	4.26	3.78	3.29	2.26	1.17	5.15	0
D2S124	3.5	3.2	2.89	2.58	2.26	1.58	0.84	3.5	0
D2S382	4.31	3.93	3.54	3.14	2.74	1.91	1.02	4.31	0
D2S399	0.48	0.4	0.33	0.27	0.22	0.14	0.08	0.48	0
D2S294	4.4	4.04	3.65	3.25	2.84	2	1.07	4.4	0
D2S335	4.76	4.32	3.91	3.51	3.1	2.22	1.21	4.76	0
D2S333	1.42	1.23	1.04	0.87	0.72	0.45	0.22	1.4	0
D2S324	5.29	4.72	4.16	3.63	3.13	2.15	1.14	5.29	0
D2S384	3.85	3.52	3.17	2.82	2.45	1.69	0.89	3.85	0
D2S152	1.9	1.7	1.52	1.36	1.2	0.87	0.48	1.9	0
D2S311	-0.81	1.62	1.66	1.58	1.46	1.11	0.63	1.66	0.085
D2S155	-5.21	0.57	1.12	1.29	1.29	1.04	0.59	1.3	0.17

Haplotypes using 17 markers spanning the IGE candidate region were constructed (data not shown). The centromeric boundary was defined by a recombination event between the markers D2S156 and D2S354; whereas a recombination between the markers D2S152 and D2S311 set the telomeric boundary. These critical recombination events localized the IGE gene to a 29cM region flanked by markers D2S156 and D2S311 (Figure 1).

Over the last four decades, family studies provided two important pieces of evidence supporting the role of genetic factors in determining susceptibility to seizures: 1) familial aggregation studies have shown evidence for an increased risk for epilepsy in relatives of probands with different types of epilepsy. In two studies standardized morbidity ratios for unprovoked seizures in relatives of individuals with idiopathic childhood-onset epilepsy varied from 2.5 to 3.4 in siblings and 6.7 in offspring (Anneger et al. 1982; Ottman et al. 1989); and 2) the presence of higher concordance rates for epilepsy in monozygotic than in dizygotic twins. Different studies showed concordance rates varying from 54 to 11 % in monozygotic twins and 10 to 5% in dizygotic pairs (Inouye 1960; Lennox, 1960; Harvald and Hauge 1965; Corey et al. 1991; Silanpaa et al 1991).

It is now generally accepted that seizure susceptibility probably reflects complex interactions of multiple factors affecting neuronal excitability and that most common genetic epilepsies display familial aggregation patterns that are not explained by segregation of a single autosomal gene (Andermann 1982; Ottman et al. 1995). This of course significantly makes more complex one's ability to isolate genes which predispose or induce epilepsy. However, some specific epileptic syndromes, which aggregate in families, may result from definable monogenic abnormalities. These families present a unique opportunity to

rapidly map genes that play a role in determining predisposition to seizures.

To date, there are a total of six loci (Greenberg et al. 1988; Leppert et al 1989; Lewis et al. 1993; Elmslie et al. 1997; Guipponi et al. 1997; Wallace et al. 1998), for which three genes have been identified in specific IGE syndromes (Bievert et al. 1998; Singh et al. 1998; Wallace et al. 1998). Interestingly, all three genes are ion channels, including a mutation found in the Na⁺-channel (1 in a Tasmania family with febrile seizures and generalized epilepsy (Wallace et al. 1998). While the candidate interval identified in our kindred remains large, a number of interesting genes map to the region. These include a cluster of Na⁺ channel genes and K⁺ channel genes (electronic data base search), as well as the GAD1 gene, which encodes for glutamate decarboxylase, an enzyme involved in the syntheses of γ -aminobutyric acid (GABA) (Bu and Tobin 1994). GABA is one of the major neurotransmitters involved in synaptic inhibition in the central nervous system (Barnard et al. 1987). However, the large size of the candidate interval will require further refinement of the locus prior to the identification of the gene responsible for IGE in the kindred studied herein.

Fifty-three % (9/17) of affected individuals in the large IGE family described herein, who had their seizures classified, had only febrile convulsions. However, 41 % of patients (7/17) presented with different types of generalized seizures. These findings may indicate that, although the predisposition to IGE in this family is determined by a single gene localized on ch2q23-q31, the different types of generalized seizures occurring in the same family may have resulted from interactions among genetic and/or environmental modifiers.

In conclusion, a locus for IGE was mapped on ch 2q23-q31. This locus seems to be associated with a specific IGE syndrome, FS

+. However, the relationship of FS+ with other IGE phenotypes, and the role of the ch 2q locus in other FS+ families and in other forms of IGE are still undetermined.

Having identified a locus for IGE on chromosome 2q23-q31, it was next verified whether mutations and/or polymorphisms could be linked to epilepsy. Public data bases were screened to identify potential genes in that chromosome region. The blasts of the data bases were also oriented to identify more specifically, membrane channels since seizures in mice and human are known to be associated with membrane channels. Having identified membrane channel coding sequences or parts thereof by the computer searches, the candidate genes, potentially involved in epilepsy, had to be validated as susceptibility genes for the disease. Two approaches were used. The first one was to test the candidate genes for mutations in a family comprising members having the disease (data not shown). The second approach was as follows. Since it is known that epilepsy results from a lower seizure threshold, and that generalized epilepsy results, in many instances, from a generalized lowering of the seizure threshold, the following hypothesis was formulated. The gene which results in epilepsy in the large family (that enabled the focusing chromosome 2q23-q31) should have other, less severe, mutations that would cause epilepsy in people who have only a weak family history of epilepsy. The sodium channel genes were chosen because they are involved in key electrical functions and could thus be good candidates. To formally test the hypothesis, many (60 to 70) unrelated cases of epilepsy were tested for mutations in these candidate genes. Surprisingly, mutations were found in all three candidate genes.

In order to assess whether mutations/polymorphisms could be identified and correlated to epilepsy, a panel of 70 to 80 epileptic patients (IGE) were tested for mutations in SCN1A, SCN2A and SCN3A,

using Single-strand conformation polymorphism (SSCP). SSCP analysis enables the detection of mutations as small as single-base substitutions. Indeed, such substitutions, by altering the conformations of single-strand DNA molecules, affect the electrophoretic mobilities thereof in non-denaturing gels. Thus, one can distinguish among sequences by comparing the mobilities of wild type (wt), mutant DNA, or different alleles of a given locus. The identification of single base substitutions of genes using SSCP is well known in the art, and numerous protocols are available therefor. A non-limiting example thereof includes fluorescence-based SSCP analysis, following PCR carried out using fluorescent-labeled primers specific for the DNA regions one wishes to amplify.

Upon the identification of differences between normal and epileptic mobilities for one of the SCNA loci of the present invention, the amplified fragments were sequenced and the nucleic acid sequences between a normal patient and an epileptic patient (IGE) compared. This comparison enabled the identification of mutations in SCN1A, SCN2A, and SCN3A. To assess, whether this difference in sequence or mutation was significantly associated with the disease, SSCP analysis was performed once again using a large cohort of normal patients. This analysis enabled to show that the mutations identified by SSCP and confirmed by sequence analysis were not present in the large cohort of normal patients tested, thereby showing that the mutations identified correlated with IGE, for the population tested.

Taken together, these results show that SCN1A, SCN2A and SCN3A are validated genes associated with epilepsy and more specifically with IGE.

This invention now establishes, for the first time, that SCN1A, SCN2A, and SCN3A, is directly responsible for idiopathic generalized epilepsy (IGE) in certain human populations. Further, this

discovery suggests that compounds which modulate the activity of SCN1A, SCN2A and SCN3A may have application far beyond the small groups of families with IGE, and may have applicability for treating many or all forms of epilepsy and related neurological disorders. It is therefore
5 an object of this invention to provide screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. This invention also claims those compounds, the use of these compounds in treating epilepsy and related neurological disorders, and any use of any
10 compounds identified using such a screening assay in treating epilepsy and related neurological disorders.

Generally, high throughput screens for one or more SCN1A, SCN2A or SCN3A (herein collectively called SCNA) sodium channels modulators i.e. candidate or test compounds or agents (e.g.,
15 peptides, peptidomimetics, small molecules or other drugs) may be based on assays which measure biological activity of SCNA. The invention therefore provides a method (also referred to herein as a "screening assay") for identifying modulators, which have a stimulatory or inhibitory effect on, for example, SCNA biological activity or expression, or which
20 bind to or interact with SCNA proteins, or which have a stimulatory or inhibitory effect on, for example, the expression or activity of SCNA interacting proteins (targets) or substrates.

Examples of methods available for cell-based assays and instrumentation for screening ion-channel targets are described in the
25 review by Gonzalez et al. (Drug Discov. Today 4:431-439, 1999), and high-throughput screens for ion-channel drugs are described in review by Denyer et al. (Drug Discov. Today 3:323-332, 1998). Such assays include efflux of sodium or related ions that can be measured in a cell line (recombinant or non-recombinant) using fluorescence-based assays using

both sodium indicator dyes and voltage sensing dyes. Preferred assays employ ^{14}C guanidine flux and/or sodium indicator dyes such as SBFI and voltage sensing dyes such as DiBAC. Oxonal dyes such as DiBAC₄ are responsive to membrane depolarization. Hyper-polarization results in
5 removal of the dye from the cell by passive diffusion, while depolarization results in concentration of the dye within the cell.

In one embodiment, the invention provides assays for screening candidate or test compounds which interact with substrates of a SCNA protein or biologically active portion thereof.

10 In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a SCNA protein or polypeptide or biologically active portion thereof.

In one embodiment, an assay is a cell-based assay in
15 which a cell which expresses a SCNA protein or biologically active portion thereof, either natural or recombinant in origin, is contacted with a test compound and the ability of the test compound to modulate SCNA biological activity, e.g., modulation of sodium efflux activity, or binding to a sodium channel or a portion thereof, or any other measurable biological
20 activity of SCNA is determined. Determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the release of a neurotransmitter or other compound, from a cell which expresses SCNA such as a neuronal cell, e.g. a substantia nigra neuronal cell, or a cardiac cell upon exposure of the test compound
25 to the cell. Furthermore, determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the change in current or the change in release of a neurotransmitter from a cell which expresses SCNA upon exposure to a test compound. Currents in cells can be measured using the patch-clamp technique as

described in the Examples below using the techniques described in, for example, Hamill et al. 1981 *Pfluegers Arch.* 391:85-100. Alternatively, changes in current can be measured by dye based fluorescence assays described below.

5 Determining the ability of the test compound to modulate binding of SCNA to a substrate can be accomplished, for example, by coupling the SCNA agent or substrate with a radioisotope or enzymatic label such that binding of the SCNA substrate to SCNA can be determined by detecting the labeled SCNA substrate in a complex. For
10 example, compounds (e.g., SCNA agents or substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting radio-emission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase or alkaline phosphatase. In these assays,
15 compounds which inhibit or increase substrate binding to SCNA are useful for the therapeutic objectives of the invention.

It is also within the scope of this invention to determine the ability of a compound (e.g. SCNA substrate) to interact with SCNA without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with SCNA without the labeling of either the compound or the SCNA (McConnell H.M. et al. (1992), Science 257:1906-1912). As used herein, a "microphysiometer" (e.g., Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and SCNA.

Modulators of SCNA can also be identified through the changes they induce in membrane potential. A suitable instrument for

measuring such changes is the VIPR™ (voltage ion probe reader) from Aurora Biosciences. This instrument works together with a series of voltage-sensing ion probe assays. The probes sense changes in transmembrane electrical potential through a voltage-sensitive FRET
5 mechanism for which the ratio donor fluorescence emission to acceptor fluorescence emission reveals the extent of cell depolarization for both sodium and potassium channels. Depolarization results from transport of a quencher across the membrane and far enough away from a membrane-bound fluorescence emitter to relieve the initial quenching and
10 produce light at the emission wavelength of the emitter. The system follows fluorescence at two wavelengths, both the intensities and ratios change during cell depolarization. The reader permits detection of sub-second, real-time optical signals from living cells in a microplate format. The system is amenable to manual operation for assay development or
15 automation via robots for high-throughput screening.

In another embodiment, the assay is a cell-based assay comprising a contacting of a cell containing a target molecule (e.g. another molecule, substrate or protein that interacts with or binds to SCNA) with a test compound and determining the ability of the test
20 compound to indirectly modulate (e.g. stimulate or inhibit) the biological activity of SCNA by binding or interacting with the target molecule. Determining the ability of the test compound to indirectly modulate the activity of SCNA can be accomplished, for example, by determining the ability of the test compound to bind to or interact with the target molecule
25 and thereby to indirectly modulate SCNA, to modulate sodium efflux, or to modulate other biological activities of SCNA. Determining the ability of the SCNA protein or a biologically active fragment thereof, to bind to or interact with the target molecule can be accomplished by one of the methods described above or known in the art for determining direct

binding. In a preferred embodiment, determining the ability of the test compound's ability to bind to or interact with the target molecule and thereby to modulate the SCNA protein can be accomplished by determining a secondary activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g. intracellular Ca^{2+} , diacylglycerol, IP3, and the like), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target -responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, such as luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter. Alternatively, recombinant cell lines may employ recombinant reporter proteins which respond, either directly or indirectly to sodium efflux or secondary messengers all as known in the art.

In yet another embodiment, an assay of the present invention is a cell-free assay in which a SCNA protein or biologically active portion thereof, either naturally occurring or recombinant in origin, is contacted with a test compound and the ability of the test compound to bind to, or otherwise modulate the biological activity of, the SCNA protein or biologically active portion thereof is determined. Preferred biologically active portions of the SCNA proteins to be used in assays of the present invention include fragments which participate in interactions with non-SCNA molecules, (e.g. other channels for sodium, potassium or Ca^{+} or fragments thereof, or fragments with high surface probability scores for protein-protein or protein-substrate interactions). Binding of the test compound to the SCNA protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the SCNA protein or biologically active portion thereof

with a known compound which binds SCNA to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a SCNA protein, wherein determining the ability of the test compound to interact with a SCNA
5 protein comprises determining the ability of the test compound to preferentially bind to SCNA or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a SCNA protein or biologically active portion thereof is contacted
10 with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the SCNA protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished, for example, by determining the ability of the SCNA protein
15 to bind to a SCNA target molecule by one of the methods described above for determining direct binding. Determining the ability of the SCNA protein to bind to a SCNA target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA, Sjolander, S. and Urbaniczky, C. (1991) Anal. Chem. 63:2338-2345
20 and Szabo et al. (1995) Curr. Opin. Struct. Biol. 5:699- 705). As used herein, "BIA" refers to a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g. BIA core). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological
25 molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished by determining the ability of the test compound to modulate the activity of an upstream or downstream effector of a SCNA target

molecule. For example, the activity of the test compound on the effector molecule can be determined or the binding of the effector to SCNA can be determined as previously described.

The cell-free assays of the present invention are
 5 amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g. a sodium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such
 10 solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n- dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl- N -methylglucamide, Triton® X-100, Triton®X-114, Thesit®, Isotridecypoly(ethylene glycol ether)n. 3-[(3- cholamidopropyl)dimethy- amino]-l-propane sulfonate (CHAPS), 3-[(3-
 15 cholamidopropyl)dimethylamino]-2-hydroxy-l-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammnonio-l-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either SCNA or its target molecule to facilitate separation of complexed from
 20 uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a SCNA protein or interaction of a SCNA protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants.
 25 Examples of such vessels include microtitre plates, test tubes and micro-centrifuge tubes. In one embodiment a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example. glutathione-S-transferase/SCNA fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto

glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or SCNA protein and the mixture incubated under conditions conducive to complex formation (e.g. at physiological conditions for salt and pH). Following incubation the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of SCNA binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices (and well-known in the art) can also be used in the screening assays of the invention. For example, either a SCNA protein or a SCNA target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated SCNA protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with SCNA protein or target molecules but which do not interfere with binding of the SCNA protein to its target molecule can be derivatized to the wells of the plate, and unbound target or SCNA protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST -immobilized complexes, include immunodetection of complexes using antibodies reactive with the SCNA protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the SCNA protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate vesicular traffic and protein transport in a cell, e.g. a neuronal or cardiac cell using the assays described in for
5 example Komada M. et al. (1999) *Genes Dev.* 13(11):1475-85, and Roth M.G. et al. (1999) *Chem. Phys. Lipids.* 98(12):141-52.

In another preferred embodiment candidate, or test compounds or agents are tested for their ability to inhibit or stimulate or regulate the phosphorylation state of a SCNA channel protein or portion
10 thereof, or an upstream or downstream target protein, using for example an *in vitro* kinase assay. Briefly, a SCNA target molecule (e.g. an immunoprecipitated sodium channel from a cell line expressing such a molecule), can be incubated with radioactive ATP, e.g., [γ - ^{32}P] - ATP, in a buffer containing MgCl_2 and MnCl_2 , e.g., 10 mM MgCl_2 and 5
15 mM MnCl_2 . Following the incubation, the immunoprecipitated SCNA target molecule (e.g. the sodium channel), can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the auto radiograph indicates that the
20 SCNA substrate, e.g., the sodium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the SCNA substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The
25 products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in, for example, Tamaskovic R. et al. (1999) *Biol. Chem.* 380(5):569-78.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to associate with (e.g. bind) calcium, using for example, the assays described in Liu L. (1999) Cell Signal. 11(5):317-24
5 and Kawai T. et al. (1999) Oncogene 18(23):3471-80.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate chromatin formation in a cell using for example the assays described in Okuwaki M. et al. (1998) J. Biol.
10 Chem. 273(51):34511-8 and Miyaji- Yamaguchi M. (1999) J. Mol. Biol. 290(2): 547-557.

In yet another preferred embodiment candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cellular proliferation, using for
15 example, the assays described in Baker F.L. et al. (1995) Cell Prolif. 28(1):1-15, Cheviron N. et al. (1996) Cell Prolif. 29(8):437-46. Hu Z. W. et al. (1999) J: Pharmacol. Exp. Ther. 290(1):28-37 and Elliott K. et al. (1999) Oncogene 18(24):3564-73.

In a preferred embodiment, candidate or test
20 compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to regulate it's association with the cellular cytoskeleton. Using for example, the assays similar to those described in Gonzalez C. et al. (1998) Cell Mol. Biol. 44(7):1117-27 and Chia C.P. et al. (1998) Exp. Cell Res. 244(1):340-8.

25 In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. et al. (1985) J. Biol. Chem. 260(8):4740-4 and Barker J.L. et al. (1984) Neurosci. Lett. 47(3):313-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cytokine signaling in a cell, (e.g., a neuronal or cardiac cell), the assays described in Nakashima Y. et al. (1999)J: Bone Joint Surg. Am. 81 (5):603-15.

In another embodiment, modulators of SCNA expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of SCNA mRNA or protein in the cell is determined. The level of expression of SCNA mRNA or protein in the presence of the candidate compound is compared to the level of expression of SCNA mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of SCNA expression based on this comparison. For example, when expression of SCNA mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of SCNA mRNA or protein expression. Alternatively, when expression of SCNA mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of SCNA mRNA or protein expression. The level of SCNA mRNA or protein expression in the cells can be determined by methods described herein or other methods known in the art for detecting SCNA mRNA or protein.

The assays described above may be used as initial or primary screens to detect promising lead compounds for further development. Often, lead compounds will be further assessed in additional, different screens. Therefore, this invention also includes secondary SCNA screens which may involve electrophysiological assays utilizing mammalian cell lines expressing the SCNA channels such as

patch clamp technology or two electrode voltage clamp and FRET-based voltage sensor. Standard patch clamp assays express wild type and mutant channels in *Xenopus* oocytes, and examine their properties using voltage-clamp electrophysiological recording. Wild type sodium channels
5 are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels
10 distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds.

Tertiary screens may involve the study of the identified modulators in rat and mouse models for epilepsy. Accordingly, it is within
15 the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an test compound identified as described herein (e.g., a SCNA modulating agent, an antisense SCNA nucleic acid molecule, a SCNA-specific antibody, or a SCNA-binding partner) can be used in an animal model to determine the
20 efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment (e.g. treatments of
25 different types of epilepsy or CNS disorders), as described herein.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic

library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, *Anticancer Drug Des.* 12: 145, 1997). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. USA.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994), *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261 :1303; Carrell et al. (1994) *Angew. Chem, Int. Ed Engl.* 33:2059; Carell et al. (1994) *Angew. Chem. Jnl. Ed. Engl.* 33:2061; and in Gallop et al. (1994). *Med Chem.* 37:1233. Libraries of compounds may be presented in solution (e.g.. Houghten (1992) *Biotechniques* 13:412-421). or on beads (Lam (1999) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556). bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull et al.(1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990); *Science* 249:386-390). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. USA.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91: 11422; Zuckermann et al. (1994), *J. Med. Chem.* 37:2678; Cho et al. (1993), *Science* 261 :1303; Carrell et al. (1994) *Angew. Chem Int. Ed. Engl.* 33:2059, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is recognized by the inventors that certain therapeutic agents have been identified for cardiac, muscular, chronic pain, acute pain and other disorders, and analgesics and anesthetics that are modulators of sodium channels. Use of these sodium channel modulators

for treating epilepsy and related neurological disorders also falls within the scope of this invention. In one embodiment of this invention, sodium channel blockers are modified to achieve improved transport across the blood brain barrier in order to have direct effect on neuronal SCNA proteins and genes. Descriptions of such compounds are found at
5 Hunter, JC et al. Current Opinion in CPNS Invest. Drugs. 1999 1(1):72-81; Muir KW et al. 2000. Cerebrovasc. Disc. 10(6):431-436; Winterer, G. 2000. Pharmacopsychiatry 33(5):182-8; Clare et al. 2000. Drug. Discov. Today 5(11):506-520; Taylor CP et al. 2000. Adv. Pharmacol. 39:47-98,
10 and Pugsley MK et al. 1998. Eur. J. Pharmacol. 342(1)93-104.

It is also recognized by the inventors that compounds which modulate (i.e. either upregulate or downregulate) transcription and translation of SCNA genes are useful for treating epilepsy or related neurological disorders. According to this invention, test compounds which
15 modulate the activity of promoter elements and regulatory elements of sodium channel genes are useful for treating these disorders.

In summary, based on the disclosure herein, those skilled in the art can develop SCNA screening assays which are useful for identifying compounds which are useful for treating epilepsy and other
20 disorders which relate to potentiation of SCNA expressing cells. The assays of this invention may be developed for low-throughput, high-throughput, or ultra-high throughput screening formats.

The assays of this invention employ either natural or recombinant SCNA protein. Cell fraction or cell free screening assays for
25 modulators of SCNA biological activity can use *in situ*, purified, or purified recombinant SCNA proteins. Cell based assays can employ cells which express SCNA protein naturally, or which contain recombinant SCNA gene constructs, which constructs may optionally include inducible promoter sequences. In all cases, the biological activity of SCNA can be

directly or indirectly measured; thus modulators of SCNA biological activity can be identified. The modulators themselves may be further modified by standard combinatorial chemistry techniques to provide improved analogs of the originally identified compounds.

5 Finally, portions or fragments of the SCNA cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome and thus, locate gene regions associated with
10 genetic disease (mutations/polymorphisms) related to epilepsy or CNS disorders that involve SCNA directly or indirectly; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

 The present invention is illustrated in further detail by
15 the following non-limiting examples.

EXAMPLE 1

Molecular analysis

 Genomic DNA was extracted from blood samples
20 (Sambrook et al. 1989) or lymphoblastoid cell lines (Anderson and Gusella 1984) from each individual. A panel of 210 dinucleotide (CA)_n repeat polymorphic markers with high heterozygosity (75%) were chosen from the 1993-94 Génethon map (Gyapay et al. 1994). Dinucleotide markers were spaced an average of 20 cM from each other throughout
25 the 22 autosomes.

 Genotyping of microsatellite markers was accomplished by polymerase chain reaction (PCR). The reaction mixture was prepared in a total volume of 13 μ l, using 80ng genomic DNA; 1.25 μ l 10x buffer with 1.5mM MgCl₂; 0.65 μ l BSA (2.0mg/ml); 100ng of each

oligonucleotide primer; 200mM dCTP, dGTP and dTTP; 25mM dATP; 1.5mCi [35S] dATP; and 0.5units Taq DNA polymerase (Perkin-Elmer). Reaction samples were transferred to 96 well plates and were subjected to: 35 cycles of denaturation for 30 seconds at 94°C, annealing for 30
5 seconds at temperatures varying from 55°C to 57°C depending on the specificity of the oligonucleotide primers, and elongation for 30 seconds at 72°C. PCR reaction products were electrophoresed on 6% denaturing polyacrylamide sequencing gels.

10

EXAMPLE 2

Genetic analysis

Two-point linkage analysis was carried out using the MLINK program version 5.1 from the LINKAGE computer package (Lathrop et al. 1984). Precise values for Zmax were calculated with the ILINK program from the
15 same computer package. Lod scores were generated based on an autosomal dominant mode of inheritance, 80% penetrance, disease gene frequency of 1:500 and allele frequencies for all allele markers calculated from the pedigree using the computer program ILINK (Lathrop et al. 1984).

20

EXAMPLE 3

Mutations in SCN1A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic
25 DNA are shown in Figure 2. Following PCR, SSCP analysis was performed and mutations in SCN1A were identified as follows (Figure 3):
(1) Glu1238Asp; normal: GCA TTT GAA GAT ATA; patient R10191 who has an idiopathic generalized epilepsy (IGE): GCA TTT GAC GAT ATA (found in 1 of 70 IGE patients). The mutation is thus a conservative aa

change, in the extracellular domain between III-S1 and III-S2. Furthermore, this residue is located at the junction between the TM domain and the extracellular domain. It may thus influence gating activity. The aa change between adult and neonatal isoforms is at a similar juxta-
5 TM domain position (between I-S3 and I-S4).

(2) Ser1773Tyr; normal: ATC ATA TcC TTC CTG, patient R9049 (affected with IGE): ATC ATA TmC TTC CTG :(TCC>TAC). This mutation is in the middle of IV-S6 TM domain; found in 1/70 IGE patients, and 0/150 control subjects tested. This mutation is interesting from a biological point of view
10 for a number of reasons. First, this region of SCN gene (IV-S6) has been found to play a critical role in fast inactivation of the SCN, by mutagenesis experiments in rat SCN (McPhee et al., 1998). This is highly relevant for pathophysiology of epilepsy, since this may increase neuronal hyperexcitability. Moreover, in patients with GEFs, a mutation has been
15 found in the SCNB1 subunit, causing impairment of the fast inactivation of the SCN (Wallace et al, 1999). Finally, many of the antiepileptic drugs (e.g. phenytoin, carbamazepine) primarily act by reducing the repetitive firing of neuron, which also involves fast inactivation of the SCN.

20

EXAMPLE 4

Mutations in SCN2A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 4. Following PCR, SSCP analysis was
25 performed and mutations in SCN2A were identified as follows (Figure 5):
(1) Lys908Arg: normal: TAC AAA GAA for patient numbers always preceded by R; R9782 (Patient with IGE): TAC AGA GAA. The mutation is thus a conservative aa change, located in an extracellular domain

between TM domains IIS5 and IIS6; in 1/70 IGE patients; 0/96 normal controls. The mutation involves an important component of the SCN gene, since the S5 and S6 segments are thought to form the wall of the transmembrane pore which allows the sodium to enter the cell. This may have an influence on the gating control of the pore.

(2) Leu768Val, in individuals R8197, R9062 and R9822 (all IGE patients) (found in 3/70 IGE patients and 0/65 control subjects). The mutations is in the IV-S6 component of the sodium channel, which is important in the inactivation of the channel (see above for more detail).

10

EXAMPLE 5

Mutations in SCN3A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 6. Following PCR, SSCP analysis was performed and mutations in SCN3A were identified as follows (Figure 7):

15

(1) Asn43DEL: allele 1: CAA GAT AAT GAT GAT GAG ; allele 2: CAA GAT --- GAT GAT GAG ; in open reading frame deletes 1 aa: DNDDEN->QDDDEN, in the cytoplasmic N-terminal segment; in IGE patients, the frequency of allele 1 = 131/146 (0.90); allele 2= 15/146 (0.10); for IGE patients: homozygotes (22): R3958, R9632; heterozygotes (12): R9049, R9152, R9649, R9710, R9896, R10069, R10191, R10213, R9993, R10009, R10256 . Of note, 2 patients are homozygous for the rare allele and all patients have IGE. In controls: allele 1 = 145/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes were found.

20

25

(2) normal: tgggtgaaggtag, R10670 (IGE patient): tggataaggtag, in conserved intron between 5N & 5A exons, significance uncertain.

(3) normal: ccccttatatctccaac, R10250 (IGE patient): ccccttatayctccaac; in conserved intron between 5N & 5A exons, significance uncertain.

- (4) Val1035Ile: normal: AAA TAC GTA ATC GAT, R9269 (IGE patient): AAA TAC RTA ATC GAT ; (GTA>ATA = Val>Ile). The mutation is thus a conservative aa change which destroys a SnaBI site (this could thus be used as a polymorphism identifiable by restriction enzyme digestion). In
- 5 SCN1A, this Val is a Ile, therefore probably not a causative mutation. In cytoplasmic domain bw II-S6 & III-S1 TMs; found in 1/70 IGE alleles; and 0/70 controls.

EXAMPLE 6

10 **SCN1A is involved in idiopathic
generalized epilepsy**

- The assumption that SCN1A gene is involved in idiopathic generalised epilepsy in humans is based on many sets of evidence. First, a mutation has been found in a large Australian family
- 15 with autosomal dominant epilepsy. The phenotype is idiopathic generalised epilepsy that is associated with febrile seizures (GEFS syndrome). The gene for this family has been previously mapped to the long arm of chromosome 2. The maximum lod score is 6.83 for marker D2S111. The candidate region is very large, spanning 21cM between
- 20 markers D2S156 and D2S311. However, within this interval, there is a cluster of sodium channel genes, including SCN1A which was hypothesized to be a candidate gene for the disease.

- Screening by SSCP of a small panel of three (3) affected patients from the family, and 3 normal controls was carried-out at
- 25 first. All the exons of the SCN1A gene have been amplified by PCR, and a SSCP variant in exon 4 was found for all of the affected individuals, and none of the controls. By sequencing an affected patient and a control, an A-T substitution at nucleotide 565 was found. This variation destroys a BamHI restriction site, this enzyme was thus used as a diagnostic test to

screen all the affected patients from the family, as well as more control cases. All affected patients from the family have A565T substitution, and none of the unaffected patients in the same kindred. An A565T substitution was not found in more than 400 control chromosomes.

5 The A565T substitution correspond to a non-conservative amino acid change (D188V). This amino acid is conserved in all sodium channels thus far identified, in all species. The only exception is SCN2A identified in rat by Numa et al, where the aspartic acid is replaced by asparagine. However, it is likely that this represents
10 an error during replication of cDNA, since other investigators have cloned the same gene in rat and found that the aspartic acid is conserved at position 188. Moreover, the same group has shown that D188N has a functional effect on channel activation in oocytes (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Of note, this A565T substitution has not
15 been found in 150 epileptic patients and in 200 control patients. Thus, this substitution has yet to be identified after 700 chromosomes assessments.

In view of proving that D188V in SCN1A, identified in the large Australian family studied, is a pathogenic mutation, the oligonucleotide mismatch mutagenesis technique was used to introduce
20 the mutation in rat SCN1A clone. RNA was isolated from mutant and wild-type clones, and injected into oocytes in view of recording sodium currents by the patch-clamp technique. The amplitude of the currents was dramatically reduced for the mutant. Also, a small shift in the inactivation curve was observed for the mutant, as compared to the wild-type. Taken
25 together, these preliminary results confirm a functional effect of D188V mutation on SCN1A gene. (more detail below).

The results presented herein are corroborated by studies from other investigators. For example, several other groups have also found linkage to the same locus on chromosome 2 for families with

GEFS or very similar syndromes. Mutations in SCN1A (Thr875Met mutation; Arg1648His) have been found to be the cause of the epileptic syndrome in at least two (2) of these families (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Also, GEFS syndrome has been shown to
5 be caused by mutation in SCN1B gene. It is demonstrated that the beta subunits interact with alpha subunits of voltage-gated sodium channels to alter kinetics of sodium currents in cells. These data suggest a common mechanism for generating abnormal neuronal discharges in the brain of patients with idiopathic generalised epilepsy.

10 Finally, in the process of screening patients from the large kindred with GEFS described above, a large cohort of patients with idiopathic generalised epilepsy was also screened by SSCP. Two (2) SSCP variants, that were subsequently sequenced were thereby identified. The variation observed are shown in Table 3:

Table 3

exon	DNA variation	IGE alleles	Control alleles
1Ax17	Glu1238Asp; conservative AA change in extracellular domain between III-S1 and III-S2	3/254	0/284
1Ax24.2	Ser1773Tyr; middle of IV-S6 TM domain	1/252	0/334

Previous functional studies have shown that amino acid substitution in the IV-S6 transmembrane domain of SCN2A significantly affects the rate of inactivation of the channel. It is thus likely that Ser1773Tyr will have an effect on the SCN1A gene function. Such functional studies are currently underway.

EXAMPLE 7

Further validation of the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE and epilepsy in general

A number of methods could be used to further validate the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE. For example, additional patients could be screened for mutations in SCN1A, SCN2A, or SCN3A. Furthermore, additional normal patients could be screened in order to validate that the mutations identified significantly correlate with disease, as opposed to reflecting a polymorphism which is not linked to IGE. Polymorphisms which are not directly linked to IGE, if in linkage disequilibrium with a functional mutation

linked to IGE, could still be useful in diagnosis and/or prognosis assays. In addition, functional studies can be carried. Numerous methods are amenable to the skilled artisan. One particularly preferred functional assay involves the use of *Xenopus* oocytes and recombinant constructs
5 harboring normal or mutant sequence of SCN1A, SCN2A, or SCN3A. *Xenopus* oocytes have been used in functional assays to dissect the structure-function relationship of the cyclic AMP-modulated potassium channel using recombinant KCNQ2 and KCNQ3 (Schroeder et al., 1998). As well, it has been used to dissect the structure-function relationship of
10 the beta subunit of the sodium channel (SCN1B gene; Wallace et al. 1998).

One such example of functional studies was investigated by assessing the effects of mutation D188V in the SCN1A gene on sodium channel function by introducing the mutation into a cDNA
15 encoding the rat ortholog SCN1A gene. This rat gene shares > 95% identity with the human SCN1A gene. The expression of wild type and mutant channels in *Xenopus* oocytes, and the examination of their properties using voltage-clamp electrophysiological recording is amenable to this *Xenopus* system. Wild type sodium channels are closed at
20 hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed
25 throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds. Among the channel properties that are likely to be altered by mutations linked to epilepsy are: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels; 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. Preliminary results indicate that D188V mutant channels are identical to wild type channels with respect to the voltage-dependence of activation and to inactivation time course. However, steady state inactivation for the mutant channels is shifted to membrane potentials that are slightly more positive than observed in wild type channels. This positive shift should increase the fraction of channels available to open at rest. This could increase neuronal excitability and contribute to epileptogenesis. Thus, a functional consequence of a naturally occurring mutation in a sodium channel gene has been tentatively identified. Thus, the functional consequence of the D188M mutant could at least in part explain its role in epilepsy. Such a functional consequence is expected to be observed with other mutations identified above in SCNA1, SCNA2 and SCNA3.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

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WHAT IS CLAIMED IS:

1. A method of determining an individual's predisposition to epilepsy and/or development of epilepsy, as well as
5 predicting this individual's response to medication, said method comprising the step of determining the genotype of at least one gene selected from SCN1A, SCN2A and SCN3A of the individual, or of a DNA variant, equivalent, or mutation which shows a linkage disequilibrium therewith, thereby determining an individual's predisposition to epilepsy
10 and/or development of epilepsy.
2. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises restriction endonuclease digestion.
3. The method of claim 1 or 2, wherein the step of
15 determining the SCN1A, SCN2A or SCN3A genotype comprises hybridizing with allele specific oligonucleotides.
4. The method of claim 1, which further comprises a step, prior to determining the SCN1A, SCN2A or SCN3A genotype, of amplifying a segment of the the SCN1A, SCN2A or SCN3A using
20 polymerase chain reaction.
5. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises a sequencing of SCN1A, SCN2A or SCN3A , or parts thereof.
6. The method of claim 1, wherein the SCN1A,
25 SCN2A or SCN3A genotype is determined using a polymorphic variant

site in linkage disequilibrium with at least one allelic variant or mutant identified in accordance with the present invention.

7. An assay for screening a test agent and selecting an agent which modulates inactivation of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying a function of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the inactivation of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

8. An assay for screening a test agent and selecting an agent which modulates the activity of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying the activity of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the activity of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

9. A method of using specific alleles of the SCN1A, SCN2A or SCN3A genes, or a variant, equivalent, or mutation thereof which shows linkage disequilibrium therewith, to set-up a screening assay

for agents destined to modulate sodium channel function for the purpose of identifying agents having an application in epilepsy therapy.

10. A method for identifying, from a library of
5 compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising:

- a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;
- 10 b) contacting said screening assay with a test compound; and
- c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

15

11. The method of claim 10, wherein the test compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide further analogs of said test compound also having said therapeutic effect.

20

12. A compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising,

- a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;
- 25 b) contacting said screening assay with a test compound; and
- c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

13. The compound of claim 12, wherein the
5 compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide analogs of said compound also having said therapeutic effect.

*1/21***Ch 2q23-q31****Centromere**

1cM	D2S142
	D2S284
4cM	
4cM	D2S156/
	D2S354
	D2S111
5cM	
	D2S294
2cM	
	D2S335

IGE locus

6cM		29 cM
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2cM	D2S324
	D2S384
2cM	
	D2S152

8cM

Telomere**D2S311**Fig 1

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1Ax00.1

NaC-340 TGTGTTCTGCCCCAGTGAGACT,
NaC-341 CTCCTGCTCTGCCCAAACCTGAAT
257 bp 53.4C

1Ax00.2

NaC-342 GGCGATGTAATGTAAGGTGCTGTC,
NaC-343 GTGCCTTCAGTTGCAATTGTTTCAG
259 bp 54.5C

1Ax01.1

NaC-268, TTAGGAATTTTCATATGCAGAATAA,
NaC-269 TGGGCCATTTTTCGTCGTC
201 bp 50.9C

1Ax01.2

NaC-270 GAAAGACGCATTGCAGAAGAAAAGG,
NaC-271 CTATTGGCATGTGTTGGTGCTACA
277 bp 54.4C

1Ax02

NaC-45 GTGCTGGTTTCTCATTTAACTTTAC,
NaC-46 TTCCCAACTTAATTTGATATTTAGC
319 bp 49.9C

1Ax03

NaC-87, GCAGTTTGGGCTTTTCAATGTTAG,
NaC-88, GACACAGTTTCARAATCCCRAATG
234 bp 48.9C

1Ax04

NaC-63, TTAGGGCTACGTTTCATTTGTATG,
NaC-64, AGCACTGATGGAAAACCAAACCTAT
338 bp 50.8C

1Ax05

NaC-164 AGCCCATGCAGTAATATAAATCCT,
NaC-165 TCCAGGCTGATAAGCTATGTCTAA
488 bp 52.8C



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1Ax06

NaC-276, CTGTGGCCTGCCTGAGCGTATT,
NaC-277 CCAATTCTACTTTTAAAGGAAATG
248 bp 50.3C

1Ax07

NaC-272, AAATACTTGTGCCTTTGAA,
NaC-273, GTACATACAATATACACAGATGC
240 bp 46.7C

1Ax08

Nac-89, AGGCAGCAGAACGACTTGTAATA,
NaC-90, ATCCGGTTTTAATTTCATAACTCA
267 bp 51.9C

1Ax09.2

NaC-217 GTTGAGCACCCCTTAGTGAATAATA,
NaC-218 TCACACGCTCTAGACTACTTCTCT
337 bp 52.7C

1Ax10a NaC-29, TGCAAATACTTCAGCCCTTTCAA,
NaC-30, TTCCCCACCAGACTGCTCTTTC
239 bp 55.1C

1Ax10a


NaC-31, GCAGCAGGCAGGCTCTCA,
NaC-32, TCTCCCATGTTTTAATTTTCAACC
293 bp 54.5C

1Ax10b

NaC-67, ATAATCTTGCAAAATGAAATCACA,
NaC-68, ATCCGGGATGACCTACTGG
307 bp 53.7C

1Ax10b

NaC-65, GATAACGAGAGCCGTAGAGATTCC,
NaC-66, AGCCAGCCATGCCTGAACTA
282 bp 56.4C

 *(cont'd)*

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1Ax10c

NaC-39, TGTTTGCTTGTCATATTGCTCAA,

NaC-40, TGCACTATTCCCAACTCACAAA

286 bp 50.7C

1Ax11.1

NaC-69 AAGGGTGTCTCTGTAACAAAAATG,

NaC-70, GTGATGGCCAGGTCAACAAA

269 bp 50.8C

1Ax11.2

NaC-71 CTGGGACTGTTCTCCATATTGGTT,

NaC-72, TTTGCAGGGGCCAGGAAG

294 bp 53.3°C

1Ax12

NaC-41 CATTGTGGGAAAATAGCATAAGC,

NaC-42, GCAAGAACCCTGAATGTTAGAAA

334 bp 51.2C

1Ax13.1

NaC-92 TAATGCTTTTAAGAATCATACAAA,

NaC-93, CCAGCGTGGGAGTTGACAATC

256 bp 51.1C

1Ax13.2

NaC-75 CGGCATGCAGCTCTTTGGTA,

NaC-91, ATGTGCCATGCTGGTGTATTTC

277 bp 55.6C

1Ax14.1

NaC-79 CACCCATCTTCTAATCACTATGC,

NaC-80, CAGCAATTTGGAGATTATTCATT


254 bp 50.4C

1Ax14.2

NaC-81 GCAGCCACTGATGATGATAA,

NaC-82, CTGCCAGTTCCTATACCACTT

269 bp 49.4C

 - 2 (cont'd)

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1Ax14.3

NaC-83 TACAGCAGAAATTGGGAAAGAT,
NaC-84, GTATTCATACCTACCCACACCTAT
269 bp 50.2C

1Ax15

NaC-202 TTCTTGGCAGGCAACTTATTACC,
NaC-203 TAAGCTGCACTCCAAATGAAAGAT
233 bp 53.1C

1Ax16.1

NaC-187, GGCTGAATGTTTCCACAACCT,
NaC-168 GTTCAACTATTTCGGAAACACG
277 bp 51.4C

1Ax16.2

NaC-188, AGGCAGAGGAAAACAATGG,
NaC-189, ACAAGGTGGGATAATTAAAAATG
234 bp 50.3C

1Ax17

NaC-143, GTTTCTCTGCCCTCCTATTCC,
NaC-144, AAGCTACCTTGAACAGAGACA
330 bp 48.8C

1Ax18


NaC-139, AATGATGATTCTGTTTATTA,
NaC-140, AATTGCCATTCCCTTTTG
272 bp 46.1C

1Ax19.1

NaC-219 TTGACATCGAAGACGTGAATAATC,
NaC-220 CCATCTGGGCTCATAAACTTGTA
285 bp 49.3C

1Ax20

NaC-338 CCCTTTGAAAATTATATCAGTAA,
NaC-339 ATTTGGTCGTTTATGCTTTATTC
230 bp 47.6C

 - 2 (cont'd)

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1Ax21

NaC-252, TCCAGCACTAAAATGTATGGTAAT,

NaC-253, ATTTGGCAGAGAAAACACTCC

261 bp 49.8C

1Ax22

NaC-254, TTTTAGCCATCCATTTTCTATTTT,

NaC-255, TATTTTCCCCCATATCATTGA

223 bp 49.1C

1Ax23.1

NaC-256 TTTGCAAGAACTAGAAAGTC,

NaC-257 TTGATGCGTGACAAAATGG

250 bp 48.3C

1Ax23.2

NaC-258 GACCAGAGTGAATATGTGACTACC,

NaC-259 CTGGGATGATCTTGAATCTAATC

246 bp 49.5C

1Ax24.1

NaC-221 GCAACTCAGTTCATGGAATTTGAA,

NaC-222 CTTGTTTTCGTTTTAAAGTAGTA

289 bp 56.1C

1Ax24.2

NaC-213 CAAAGATCACCTGGAAGCTCAGTT,

NaC-223 TTCAAGCGCAGCTGCAAAGTGAAT

277 bp 55.8C

1Ax24.3

NaC-260 ACATCGGCCTCCTACTCTTCCTA,

NaC-261 ACAGATGGGTTCCCACAGTCC


268 bp 55.3C

1Ax24.4

NaC-262 TAACGCATGATTTCTTCACTGGTT,

NaC-263 ATCCCAAAGATGGCGTAGATGA

262 bp 54.9C

 *(cont'd)*

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1Ax24.5

NaC-308, TGAGAAATAGGCTAAGGACCTCTA,

NaC-309 CCTAGGGGCTGGATTCC

244 bp 53.2C

1Ax24.6

NaC-310, AAGGGGTGCAAACCTGTGATTTT,

NaC-311 AGGGCCATGTGGTTGCCATAC

252 bp 53.4C

1Ax24.7

NaC-312 CTTCCGGTTTATGTTTTTCATTTCT,

NaC-313 TCTTTATTAGTTTTGCACATTTTA

278 bp 48.4C

1Ax24.8

NaC-364 CAATCCTTCCAAGGTCTCCTATC,

NaC-365 TTTCATCTTTGCCTTCTTGCTCAT


326 bp 52.4C

1Ax24.9

NaC-366 CATGTCCACTGCAGCTTGTTCCA,

NaC-367 TCCCCTTTACACAGAGTCACAGTT

292 bp 53.1C

 (cont'd)

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a. Glu1238Asp:

normal: GCA TTT GAA GAT ATA;
patient R10191 with IGE: GCA TTT GAC GAT ATA.

b. Ser1773Tyr:

normal: ATC ATA TcC TTC CTG;
patient R9049 with IGE: ATC ATA TmC TTC CTG; TCC>TAC

FIG. 3

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2Ax00.1 NaC-235 ATGGGTTGAATGACTTTCTGACAT, NaC-236,
AGGCATTTCTGTACAGGGACTAC

266 bp 52.7C

2Ax00.2 NaC-237 ACAGGAAATGCCTCTTCTTACTTC, NaC-238,
TTTCCCCAAGGATTCTACTACTGT

277 bp 50.6C

2Ax01 NaC-100, AGTGCATGTAAGTACACAATCAC, NaC-101,
CTTGCGTTCCTGTTTGGGTCTCT

241 bp 53.7C

2Ax01 NaC-11 TCCGCTTCTTTACCAGGGAATC, NaC-102,
AGGCAGTGAAGGCAACTTGACTAA

259 bp 55.1C

2Ax02 NaC-96, CAGGGCAATATTTATAAATAATGG, NaC-97,
TTTGGAATAATGTGTAGCTCAATAA

289 bp 48.7C

2Ax03 NaC-43, AAGGCATGGTAGTGCATAAAAG, NaC-44,
ATGAAACATAAAGGGAGGTCAA

201 bp 49.3°C

2Ax04 NaC-47, AATGTGAGCTTGGCTATTGTCTCT, NaC-48,
ATAGGCTCCCACCAAGTGATTAC

213 bp 50.9°C

2Ax05 NaC-49, AGGCCCCTTATATCTCCAAGT, NaC-50,
CAACAAGGCTTCTGCACAAAAG

241 bp 53.9°C

2Ax05.2 NaC-110, CTTGGTGGCTTGCCTTGAC, NaC-111,
TCATGAGTGTCGCCATCAGC

223 bp 51.1C

FIG. 4

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2Ax05.3 NaC-112, GGAAAGCTGATGGCGACACT, NaC-113,
CTGAGACATTGCCCAGGTCC
329 bp 53.0C

2Ax05.4 NaC-114, TTTTACCCGTTGCTTTCTTTA, NaC-115,
TATCCCTTGCTCTTTCATTTATCT
224 bp 50.9C

2Ax06.1 NaC-169, GCCGGTAAAATAGCTGTTGAGTAG, NaC-170,
GCCATTGCAAACATTTATTTTCGTA
206 bp 53.3C

2Ax06.2 NaC-171, GCGTGTTTGCGCTAATAG, NaC-172,
CTAAGTCACTTGATTCACATCTAA
295 bp 48.0C

2Ax07 NaC-196, ACAGGGTGGCTGAAGTGTTTTA, NaC-197,
GTGGGAGGTGGCAGGTTATT
199 bp 52.6C

2Ax08 NaC-118, CAATTAGCAGACTTGCCGTTATT, NaC-119,
TCTCTTGAGTTCGGTGTTTTATGA
252 bp 52.9C

2Ax09 NaC-120, ACCGAACTCAAGAGAATTGCTGTA, NaC-121,
AAAGGACCGTATGCTTGTTCACTA
334 bp 52.9C

2Ax10a.1 NaC-161 TATGAATGCGCATTTTACTCTTTG, NaC-156,
TGGAGCTCAACTTAGATGCTACTG
286 bp 52.1C

2Ax10a.2 NaC-13 GGTGCTGGTGGGATAGGAGTTTTT, NaC-162,
TCCATTAAATTCTGGCATATTCTT
316 bp 50.9C

2Ax10b.1 NaC-145 TCAGAGGGGTGCTTTCTTCCACAT, NaC-14,
CTTCGGCTGTCATTGTCCTCAAAG
298 bp 55.6C

FIG - 4 (cont'd)

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2Ax10b.2 NaC-146, GCAAAGGACATTGGCTCTGAGAAT, NaC-147,
CTGCCTGCACCAGTCACAACTCT
324 bp 59.4C

2Ax10c NaC-190, TGGGCTTTGCTGCTTTTCAA, NaC-191,
AGTAACTGTGACGCAGGACTTTTA
218 bp 51.5C

2Ax11.1 NaC-148, CCCTGTTCTCCAGCAGATTA, NaC-70,
GTGATGGCCAGGTCAACAAA
283 bp 51.5C

2Ax11.2 NaC-149, TTTGATTTGGGACTGTTGTAAAC, NaC-150,
AAGGCAATTATAAACTCTTTCAAG
233 bp 52.0C

2Ax12 NaC-159, TGGGAGTTAAATTAAGTTGCTCAA, NaC-160,
ACATTTTATGAACACTCCCAGTTA
285 bp 50.4C

2Ax13.1 NaC-239 ATTAACACTGTTCTTGCTTTTAT, NaC-240,
GTGCCAGCGTGGGAGTTC
239 bp 51.1C

2Ax13.2 NaC-241 GTGGGGGCTCTAGGAAACCT, NaC-242,
TTTAATGAAAATGAGGAAAATGTT
324 bp 53.7C

2Ax14.1 NaC-134, GACCAAGCATTTTTATTTTCATTC, NaC-135,
AGTGGCAGCAAGATTGTCA
234 bp 49.6C

2Ax14.2 NaC-136, GGCCTTGCTTTTGAGTTCC, NaC-137,
GGTCTTTGCCTATTTCTATGGTG
257 bp 51.1C

FIG - 4 (cont'd)

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2Ax14.3 NaC-266, TTAAACCGCTTGAAGATCTAAATA, NaC-267,
TATACACCAAATATCTCCTTAT
319 bp 48.5C

2Ax15 NaC-314 GGGGCACACCTAATTAATTTTAT, NaC-315,
AAAGAGGATACTCAAGACCACATA
(247 bp) 51.5C

2Ax16 NaC-344 CCCACCAACACAAATATACCTAAT, NaC-345,
TGAAGGGAAAGGGAAAAGATT
283 bp 52.2C

2Ax17 NaC-346 TCCAGCCTTAGGCACCTGATAA, NaC-347,
ATAAAGCAGCAAAGTGCAGCATAC
310 bp 52.4C

2Ax18 NaC-348 AAGGCTGAACTGTGTAGACATTTT, NaC-349,
TGACATTTCCATGGTACAAAGTGT
262 bp 52.2C


2Ax19.1 NaC-350 TTTGTTGTTGGCTTTTCACTTAT, NaC-351,
CCACCTGGCAGTTTGATTG
268 bp 51.9C

2Ax19.2 NaC-352 TAAGCGTGGTCAACAACACTACAGT, NaC-353,
ATTCTTGCCAGCATTTATTGTC
260 bp 50.2C

2Ax20 NaC-354 CAAAACATTGCCCCAAAAG, NaC-355,
TCAAACATAACAATTTCCCTCTAA
239 bp 48.1C

2Ax21 NaC-306, GATAATTAAAACTCACTGATGTA, NaC-307,
GGAGGCTAAAGGAAAGAGTATG
288 bp 46.6C

2Ax22 NaC-356 ATTTTATAGCCAGCAAAGAACAC, NaC-357,
CTAGAAATTCGGGCTGTGAA
230 bp 49.6C

 4 (cont'd)

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2Ax23.1 NaC-358 CTGCTTTGTGACCTAAGGCAAGTT, NaC-359,
GTGACCATGTTAAGGCAGATGAGG
290 bp 51.4C

2Ax23.2 NaC-360 GGAATGGTCTTTGATTTTGTAACC, NaC-361,
TCCTTAACTGAATAAAAGCACCTC
290 bp 51.6C

2Ax24.1 NaC-207 TGGAACACCCATCAAAGAAGATACT, NaC-208,
GTGGGAGTCCTGTTGACACAAAC
278 bp 52.8C

2Ax24.2 NaC-209 AGCGATTCATGGCATCAAAC, NaC-210,
ACGTGGTGGAAGGCGTCATA
270 bp 52.9C

2Ax24.3 NaC-211 GCGACCCAGTTTATAGAGTTTGCC, NaC-212,
CTTGTTTGCGTTTCAACGTGGTC
289 bp 56.1C

2Ax24.4 NaC-213 CAAAGATCACCCCTGGAAGCTCAGTT, NaC-214,
ATCCAGGGCATCTGCAAAATCAGAA
277 bp 55.8C

2Ax24.5 NaC-215 TGCCTATGTTAAGAGGGAAGTTGGG, NaC-216,
ATGACCGCGATGTACATGTTTCA
279 bp 55.3C

2Ax24.6 NaC-278 TCAATTGTTTACAGCCCGTGATG, NaC-279,
TTTATACAAAGGCAGACAACAT
302 bp 52.0C

2Ax24.7 NaC-280 AGGCGTAATGGCTACTCAGACGA, NaC-281,
GTAATCCCTCTCCCCGAACATAAAC
251 bp 53.8C

2Ax24.8 NaC-282 TTTGATTCACGGGTTGTTTACTCTTA, NaC-283,
TTCTATGGAACATTTACAGGCACATT
294 bp 52.1C

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2Ax24.9 NaC-284 TAATGTGCCTGTAAATGTTCCATAGA, NaC-285,
CAGGCTTCTTAGAAAGGACTGATAGG
264 bp 50.6C

2Ax24.10 NaC-286 GTCCCAGCAGCATGACTATC, NaC-287,
CCCACTGGGTAAAATTACTAAC
249 bp 49.4C

2Ax24.11 NaC-288 TAGCCATCTTCTGCTCTTGGT, NaC-289,
TGGCTTCCCATATTAGACTTCTG
307 bp 51.3C

2Ax24.12 NaC-290 TCTTGCCTATGCTGCTGTATCTTA, NaC-291,
AGTCGGGCTTTTCATCATTGAG
207 bp 51.8C

2Ax24.13 NaC-292 TTCTTCATGTCATTAAGCAATAGG, NaC-293,
TTCAATTTAAAAGTGCTAGGAACA
299 bp 49.4C

2Ax24.14 NaC-294 CTTCAAGGTGGATGTCACAGTCACTA, NaC-295,
ATTCAAGCAATGCCAAGAGTATCA
263 bp 51.5C

2Ax24.15 NaC-296 CTTTCAATAGTAATGCCTTATCAT, NaC-297,
TCCTGCATGCATTTACCAAC
348 bp 49.6C

2Ax24.16 NaC-362 CTGTTACATTTTGTAAAATAAT, NaC-263,
ATCCCAAAGATGGCGTAGATGA
309 bp 50.8C

2Ax24.17 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-363,
GATCTTTGTCAGGGTCACAGTCT
269 bp 54.0C

FIG. 4 (cont'd)

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- a. Lys908Arg:
normal: TAC AAA GAA;
9782 (Patient with IGE): TAC AGA GAA;
- b. leu768val, in individuals 8197, 9062 et 9822 (all IGE patients).

FIG. 5

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3Ax00a.1 NaC-390 TGTGTCCGCCAGTAGATGG, NaC-391,
TTTTTGACCACAGAGGTTTACAA
233 bp 51.4C

3Ax00a.2 NaC-392 GAAGCGGAGGCATAAGCAGA, NaC-393,
GGTGCAGATAATGAAATGTTTTGT
253 bp 51.3C

3Ax00b NaC-394 CACCCCTATGCCAAATGTCAAAGA, NaC-395,
CAAAAACAAACTTATACCCAGAAG
293 bp 51.6C

3Ax00c NaC-396 CAAATATTGGGCAAACCCTAAT, NaC-397,
AAGGTGCCATCACAAAATCAT
225 bp 50.7C

3Ax01.1 NaC-51 ATCGCTTGCTTTCCTAACTCTTGT, NaC-52,
AAGTCACTATTTGGCTTTGGTTG
260 bp 53.1C

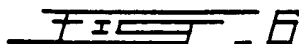
3Ax01.2 NaC-53 AGAAGCCCCAAAAAGGAACAAGATA, NaC-54,
GGCCCAGAAAAGTATATTACAGTT
231 bp 50.8C

3Ax02 NaC-85, TCCTTAAATAAGCCCATGTCTAAT, NaC-86,
TCTCAAAGAAATTTTACAGATACT
273 bp 47.3C

3Ax03 NaC-27, AATGGCCATGGTAACCTACTAACA, NaC-28,
CAGGCTATACCCACAAGGAGATT
212 bp 51.8C

3Ax04 NaC-94, TGTTAATTTTGGCTTGGATGTT, NaC-95,
TCACTCCTTTGCGCTTATCAA
198 bp 50.8C

3Ax05.1 NaC-247, AGGGCTCTATGTGCCAAACC, NaC-248,
AGGGGCCTACTACCTTACACCAG
213 bp 52.2C



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3Ax05.2 NaC-249 TGTAATCCCAGGTAAGAAGAAAC, NaC-250,
TACCGGGATGAACTGTAATAATAA
304 bp 51.8C

3Ax06.1 NaC-192, TTCTGGCACTCTTCCTCAGGTAAC, NaC-193,
GTCCCATTTGAATCCATTGTGC
261 bp 55.4C

3Ax06.2 NaC-194, GGCCCCCAAGCGATTCTG, NaC-195,
TGTACACCCACAGTCTCAACTATT
209 bp 50.3C

3Ax07 NaC-204, ACAGCCACCTTTGTAAATAA, NaC-205,
TTTTTCGCAAAGAGTTCTAT
220 bp 46.6C

3Ax08 NaC-98, AAACGTGACCCTACCTCCATTTCTC, NaC-99,
ACTCAGCCTATGCTTTTCATTTC
247 bp 53.2C


3Ax09 NaC-37 CAGATATTTATTTGGGGACATTAT, NaC-38,
AAATCTTTGCKTTTATCACTCAGT
295 bp 52.0C

3Ax10a.1 NaC-198 TAGTGCCTGGCTTTGTTTTATGAC, NaC-199,
CGGATTTGGGAAAGCTGTCTCT
225 bp 54.3C

3Ax10a.2 NaC-200 AGAGCACCTTGAAGGAAACAACAA, NaC-274,
TCCCTCAACTGAAGTACAGATAGT
253 bp 51.2C

3Ax10b NaC-33, ATAATTGCGTTCTTCCCCTACCC, NaC-34,
AAGCCCTGGCACCATCCTG
301 bp 56.2°C

3Ax10c NaC-35, TTTGCAAAGAAATGCTATGT, NaC-36,
CTGGGTAACAGACTTCAGTAAT
303 bp 51.4°C

 (cont'd)

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3Ax11.1 NaC-122, ATGGGATTGTCTTCTCAAGTTTCT, NaC-123,
GATGGCAAGATCAACAAATGGA
294 bp 50.3C

3Ax11.2 NaC-124, CTTGATCTGGGACTGCTGTGATG, NaC-125,
AGGATATAATTTTGGTTCAACA
284 bp 51.5C

3Ax12 NaC-61, TTTTCAGTGCTCTTGATAGTAGTG, NaC-62,
GTGCCAATGAGCGACAGG
254 bp 50.7°C

3Ax13.1 NaC-73, CCACGTGTGGTTCTATGATACC, NaC-74,
ACCGTGGGAGCGTACAGTCA
298 bp 52.3C

3Ax13.2 NaC-75, CGGCATGCAGCTCTTTGGTA, NaC-76,
TGGCCACGTTCCCTAGCTACTGTC
291 bp 55.9C


3Ax14.1 NaC-55, GAGTTCCCTTTTTAGGCTGTTATT, NaC-56,
TCTTATTGCCTTCATGGATTCTA
285 bp 50.5C

3Ax14.2 NaC-57, TGAAAAATAAGATGCGGGAGTG, NaC-58,
GTGAGGCTGGGGTTGTTTATG
247 bp 51.7C

3Ax14.3 NaC-59, GAGATGGGAATGGAACCACCA, NaC-60,
TTCGATAATGCATATAAGCACAA
297 bp 51.7C

3Ax15 NaC-318 AAGGGGGAAAATCACATCTTT, NaC-319,
TTAAATGAGGCATATTCAGTCTCC
235 bp 51.8C

3Ax16 NaC-116, GGAAGTGGAGTGGGGAAGG, NaC-117,
ATTCTTGCCAATATGCATTTCACT
271 bp 51.1C

 *(cont'd)*

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3Ax17 NaC-157, TTCTTTTGTACTCACTATTATACTAA, NaC-158,
AAACTTGCCTCTTTTAAAAACAAT
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3Ax18 NaC-374 TACCACACCCTATACCTTCAGTCA, NaC-375,
GAGTATGGCACCCTTTTCTATCTA
275 bp 51.4C

3Ax19.1 NaC-386 GCTATGTTCCCCTCGCTGTCT, NaC-387,
TGCTTGCCCAAGAGCCTGAC
231 bp 53.6C

3Ax19.2 NaC-388 GCTGGCAAGTTCTACCACTGTG, NaC-389,
CAAACGAAGAACATCAGGGAAATA
247 bp 53.0C

3Ax20 NaC-376 TTCACAATATTGTACAAAAAGTTA, NaC-377,
ATTACCACCAATATTCACCATAAG
230 bp 46.4C

3Ax21 NaC-378 TCAGGGTAAGGCAAAAGTAGCAC, NaC-379,
GAACCCCAAGATGAAGAAAGGTAA
294 bp 50.2C

3Ax22 NaC-380 TTTGTGAAAGTACTATTGGAACAC, NaC-381,
ACGCATGGCTTTGGAACAT
204 bp 49.6C

3Ax23.1 NaC-382 CCCGTATGTGGAAGGGCTTTAT, NaC-383,
CTAGGTTGATCCGGGACAAAATA
246 bp 52.9C

3Ax23.2 NaC-384 AACGGATGACCAGGGCAAATAC, NaC-385,
CTAGAAGGTCCTGGGGCAACTG
234 bp 54.8C

3Ax24.1 NaC-317 AAGCCATCATGTAAAGTGAAAAG, NaC-320,
ATCCCAAAGATGGCATAGATA
274 bp 52.5C

FILE - 6 (cont'd)

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3Ax24.2 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-326,
TGAGCTGCCAGGGTGAATTG
282 bp 54.9C

3Ax24.3 NaC-327 TTGCTAGCACCTATTCTTAATAGTGC NaC-328,
CCAGGGCAGCTGCAAAATCAGAG
318 bp 54.2C

3Ax24.4 NaC-329 CCCGATGCGACCCAGTTTA, NaC-330,
TGGAGGGGTTTGATGCCATA
250 bp 55.2C

3Ax24.5 NaC-331 GATGGATGCCCTTCGAATACAGA, NaC-332,
TTCCCATTAGTTTGTCAATAATC
258 bp 50.6C

3Ax24.6 NaC-321 AAGGGGAGGATTGACTTACCTAT, NaC-333,
TTGGCATGGACCTCCTCTTGA
302 bp 51.5C

FILE - 6 (*cont'd*)

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a. Asn43DEL:

9706 (allele 1; IGE patient): CAA GAT AAT GAT GAT GAG ;

9632 (allele 2; patient has IGE): CAA GAT --- GAT GAT GAG ;

allele 1 = 131/146 (0.90);

allele 2 = 15/146 (0.10);

for IGE patients: homozygotes (22): 3958, 9632; heterozygotes (12): 9049, 9152, 9649, 9710, 9896, 10069, 10191, 10213, 9993, 10009, 10256 (note that 2 patients are homozygous for the rare allele; all patients have IGE); in controls: allele 1 = 45/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes found.

b. normal: tggtgtaaggtag,

10670 (IGE patient): tggtataaggtag

c. normal: cccccttatatctccaac,

10250 (IGE patient): ccccttatayctccaac;

d. Val1035Ile:

normal: AAA TAC GTA ATC GAT,

9269 (IGE patient): AAA TAC RTA ATC GAT; GTA>ATA = Val>Ile.

FIG. 7

SEQUENCE LISTING

<110> McGill University

Rouleau, Guy A.

Lafrenière, Ronald G.

Cossette, Patrick

Ragsdale, David

<120> LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS
THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE,
PROGNOSE OR OR TREAT EPILEPSY

<130> 13180.17

<140> PCT/CA00/01404

<141> 2000-11-24

<160> 408

<170> PatentIn Ver. 2.1

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Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val Ala		
	1010	1015 1020
Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe Ile Arg		
	1025	1030 1035 1040
Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp Leu Asn Asn		
	1045	1050 1055
Lys Lys Asp Ser Cys Met Ser Asn His Thr Ala Glu Ile Gly Lys Asp		
	1060	1065 1070
Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr Ser Gly Ile Gly Thr		
	1075	1080 1085
Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp Glu Ser Asp Tyr Met Ser		

1090	1095	1100
Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly		
1105	1110	1115 1120
Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Asp Phe Ser Ser Glu Ser		
	1125	1130 1135
Asp Leu Glu Glu Ser Lys Glu Lys Leu Asn Glu Ser Ser Ser Ser Ser		
	1140	1145 1150
Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Val Glu Glu Gln Pro Val		
	1155	1160 1165
Val Glu Pro Glu Glu Thr Leu Glu Pro Glu Ala Cys Phe Thr Glu Gly		
	1170	1175 1180
Cys Val Gln Arg Phe Lys Cys Cys Gln Ile Asn Val Glu Glu Gly Arg		
	1185	1190 1195 1200
Gly Lys Gln Trp Trp Asn Leu Arg Arg Thr Cys Phe Arg Ile Val Glu		
	1205	1210 1215
His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser		
	1220	1225 1230
Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile		
	1235	1240 1245
Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe Ile		
	1250	1255 1260
Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr Tyr Phe		
	1265	1270 1275 1280
Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp Val Ser Leu		
	1285	1290 1295
Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu Leu Gly Ala Ile		
	1300	1305 1310
Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser		
	1315	1320 1325
Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Leu Gly Ala Ile		
	1330	1335 1340
Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile		

1345	1350	1355	1360
Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys	1365	1370	1375
Ile Asn Thr Thr Thr Gly Asp Arg Phe Asp Ile Glu Asp Val Asn Asn	1380	1385	1390
His Thr Asp Cys Leu Lys Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp	1395	1400	1405
Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser	1410	1415	1420
Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala	1425	1430	1435
Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Glu Ser	1445	1450	1455
Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe	1460	1465	1470
Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln	1475	1480	1485
Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln	1490	1495	1500
Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln	1505	1510	1515
Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met Val Phe Asp	1525	1530	1535
Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys	1540	1545	1550
Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Ser Glu Tyr	1555	1560	1565
Val Thr Thr Ile Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe	1570	1575	1580
Thr Gly Glu Cys Val Leu Lys Leu Ile Ser Leu Arg His Tyr Tyr Phe	1585	1590	1595
Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile			1600

1605	1610	1615
Val Gly Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro		
1620	1625	1630
Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg		
1635	1640	1645
Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met		
1650	1655	1660
Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val		
1665	1670	1675
Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys		
1685	1690	1695
Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn		
1700	1705	1710
Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly		
1715	1720	1725
Leu Leu Ala Pro Ile Leu Asn Ser Lys Pro Pro Asp Cys Asp Pro Asn		
1730	1735	1740
Lys Val Asn Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser		
1745	1750	1755
Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val		
1765	1770	1775
Val Val Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala		
1780	1785	1790
Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe		
1795	1800	1805
Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Met Glu		
1810	1815	1820
Phe Glu Lys Leu Ser Gln Phe Ala Ala Ala Leu Glu Pro Pro Leu Asn		
1825	1830	1835
Leu Pro Gln Pro Asn Lys Leu Gln Leu Ile Ala Met Asp Leu Pro Met		
1845	1850	1855
Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr		

1860 1865 1870
 Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
 1875 1880 1885
 Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln
 1890 1895 1900
 Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val
 1905 1910 1915 1920
 Ile Ile Gln Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys
 1925 1930 1935
 Gln Ala Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn
 1940 1945 1950
 Leu Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser
 1955 1960 1965
 Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro Pro
 1970 1975 1980
 Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu Gln Glu
 1985 1990 1995 2000
 Gly Lys Asp Glu Lys Ala Lys Gly Lys
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<210> 4

<211> 1246

<212> DNA

<213> Homo sapiens

<400> 4

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 ngnsartvr aktsvgktvg asvkksdvmt vcsvagmgnr nkcwnashs kntvnyngtn 180
 tvdwksydsr yhygdacgns sdagcgymcv kagrnnnygyt sdtswasrmt dwnytraagk 240
 tymvvgssyna vvamaynata kamkkaaaat atashrsaa grsdsssask ssksakrrnr 300
 rkkrrksggk ddkssdsrrk grsgnrtykr ysshssrgss rrnsrtssrg rakdvgsnda 360
 ddhstdnsrr dsrvrrhgrn snstsrssrm avangkmhst vdcngvsvsg gsvtsvgvdk 420
 atddngttdt mrkrrssshv smdsrrams astntvsrkc cwyksnwcds ywkvhvvnv 480
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 vkakswtnmk gnsvgagntv avavvgmgks ykdcvckasd crwhmndhsv rvcgwtmwdc 600
 mvagamctvm mvmvgnvna sssadnaatd ddnmnnavdr mhkgvayvkr kysrkkdkdd 660
 nnkkdscmsn htagkddykd vngttsgggtg ssvkydsdym snnstvtvav gsdhntdsss 720


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dskknsssss gstdvgavvv tactgcvrkcnvgrgkwn rrtcrvhnwt vmssgaadyd 780
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vvnagasmnv vcwsmgvnag kyhcntttgd rddvnnhtdc krntarwknv kvndnvvgys 900
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kgmvdvtrvd smcnmvtmmv tddsyvttsr nvvtgcvksr hyytgwndvv vsvgmakyvs 1020
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dcdnkvnsgs vkgdcgnsvg vsysvvvnmv avnsvatsas ddmvwwkdda tmksaaannk 1140
amdvnsgdrh cdatkrvgsg mdarmrmasn skvsytttkr kvsavrayrr hkrtvkasty 1200
nknkkggank dmdrnnstkt dtmstaacsy drvtkvkhgk dkakgk 1246

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<210> 5

<211> 850

<212> DNA

<213> Homo sapiens

<400> 5

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gcaaggagaa gcaatactgg gagattacag agaagaaagg aaaaaaggct gagagaaaag 180
aggttgagga agaaatcata aatctggatt gtgagaaagt gttaaatatt tagccactag 240
atggcgatgt aatgtaaggt gctgtcttga cttttttttt ttttttttga aacaagctat 300
ttgctgattt gtattaggta ccatagagtg aggcgaggat gaagccgaga agatactgca 360
gagggtctctg gtgcatgtgt gtatgtgtgc gtttgtgtgt gtttgtgtgt ctgtgtgttc 420
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aacaattgca actgaaggca cattgttatc atctcgtctt tgggtgatgc tgttcctcac 540
tgcagatgga taattttcct tttaatcagg taagccatct aattgtttca tcttgatttt 600
aagttttattc attccagtta ttcccttgga aaaagagtcc atggaaattc agtttgggca 660
gagcaggaag tccatttttg tatgtgtatt cagaccaact gtccccctcc tccctctcct 720
cctcttcttg tccccctccc cgcgcctcc tctctcaacc tccatgaac tgaaatcagg 780
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<210> 6

<211> 483

<212> DNA

<213> Homo sapiens

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caggacctga cagcttcaac ttcttcacca gagaatctct tgcggctatt gaaagacgca 180
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cccaaagcaa atagtgactt ggaagctgga aagaaccttc catttattta tggagacatt 300
cctccagaga tgggtgtcaga gcccctggag gacctggacc cctactatat caataagaaa 360
gtgagtgttt tttttatcag gcatattttt gctgctaatt gcctactgca ttccttgga 420
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ttt

483

<210> 7

<211> 497

<212> DNA

<213> Homo sapiens

<400> 7

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tggtttctca tttaacttta caataattta ttatgacaag taacagaaaag tagataacag 120
agtttaagtg gtttatactt tcatacttct atgttggtgt cctgtcttac agacttttat 180
agtattgaat aaaggggaag ccatcttccg gttcagtgcc acctctgccc tgtacatttt 240
aactcccttc aatcctctta ggaaaatagc tattaagatt ttggtacatt catatccttt 300
ttcaagtgat taatattaac tatttgtaca tgatctgtaa gcactttata gctaaatata 360
aaattaagtt gggaaatgtc catattatat aggtttcatc actctcattt tgcattcttg 420
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<210> 8

<211> 501

<212> DNA

<213> Homo sapiens

<400> 8

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taccctgaa ttttggctaa gctgcagttt gggcttttca atgttagctt ttgtaatat 180
aacacttgga ttttgatttt cttttgtgtg ttccttaaca ataacctaca ttattcagca 240
tgctaattat gtgcactatt ttgacaaact gtgtgtttat gacaatgagt aacctcctg 300
attggacaaa gaatgtagag taagttcaac ttatatattt aataacatat atacattygg 360
gattytgaaa ctgtgtctta atgtagtctt aaaataaaac tgaagagcat ttatttaaag 420
tcattcctag acaaaattac gcagcaagag gacaatgctc attggccctc aggccctgctg 480
gcgttatact gattatcact c                                     501

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<210> 9

<211> 563

<212> DNA

<213> Homo sapiens

<400> 9

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gaaattggta tgctatgaaa aaacactgtt actttatcaa attttttgga tgcttgtttt 240
cagatacacc ttcacaggaa tatatacttt tgaatcactt ataaaaatta ttgcaagggg 300

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attctgttta gaagatttta ctttccttcg ggatccatgg aactggctcg atttcactgt 360
 cattacattt gcgtaagtgc ctttbytga aactttaagag agaacaatagt ttggttttcc 420
 atcagtgcct atgcttttta gaatagggtt gctttacctg tagaatattt ttgtgtgatt 480
 tatacattca aactctggat ttcaatttag cacaacaaag gtctaagtgg aatttcacta 540
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<210> 10

<211> 253

<212> DNA

<213> Homo sapiens

<400> 10

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 agtcttgaga gctttgaaaa ctatttcggt aattccaggt aagaagtgat tagagtaaag 180
 gataggctct ttgtacctac agctttttct ttgtgtcctg tttttgtgtt tgtgtgtgaa 240
 ctcccgtta cag 253

<210> 11

<211> 340

<212> DNA

<213> Homo sapiens

<400> 11

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 ggcaatgtct cggcattgag aacattcaga gttctccgag cattgaagac gatttcagtc 180
 attccagggt agagcaaggt tagataatga gacggaccca tcatgtgatt cagcatcctt 240
 ctctgcttga cattcagttt tacagaaaat caggaatcat aagactaggt gttcaaagaa 300
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<210> 12

<211> 409

<212> DNA

<213> Homo sapiens

<400> 12

cacgcgtgct tagccctcat agtaatagcc tcctaccttc aggctgaaa accattgtgg 60
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 tgagcgtatt tgctctaatt gggctgcagc tgttcatggg caacctgagg aataaatgta 180
 tacaatggcc tcccaccaat gcttccttgg aggaacatag tatagaaaag aatataactg 240
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<210> 13
 <211> 266
 <212> DNA
 <213> Homo sapiens

<400> 13
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 cgactttctt ttttcaaaca ggatatcatt atttcttgga gggtttttta gatgcactac 180
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 tgtacacaat acatatgtgt atcttt 266

<210> 14
 <211> 604
 <212> DNA
 <213> Homo sapiens

<400> 14
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 gaaatagatt agttacttat ttgtcaaact tttattttga aataccaaat ctttctgact 180
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<210> 15
 <211> 378
 <212> DNA
 <213> Homo sapiens

<400> 15
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 acatgatatt ttttgtattg gtcattttct tgggctcatt ctacctaata aatttgatcc 180
 tggtgtggt ggccatggcc tacgaggaac agaatcaggc caccttgga gaagcagaac 240
 agaaagaggc cgaatttcag cagatgattg aacagcttaa aaagcaacag gaggcagctc 300
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 tagtctagag cgtgtgat 378

<210> 16
 <211> 845
 <212> DNA
 <213> Homo sapiens

<400> 16
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 cataataaat gttaccatgg agcaaaactaa attatctcca aaagccttca ttaggtagaa 180
 agaaaaaaaa aatctcctct tatacttgca gagaatcttc tctgtgagat gatcttcagt 240
 cagttcaata ttttttttaa aagccatgca aatacttcag ccctttcaaa gaaagataca 300
 gtctcttcag gtgctatggt aaaatcattt ctcttcaata tagcaggcag caacggcaac 360
 tgccctcagaa cattccagag agcccagtg agcaggcagg ctctcagaca gctcatctga 420
 agcctctaag ttgagttcca agagtgtctaa ggaaagaaga aatcggagga agaaaagaaa 480
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 aactgaatca accactggtg tggttatatt aaacccatcc ctctctcaca tagttatgca 780
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<210> 17
 <211> 965
 <212> DNA
 <213> Homo sapiens

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 accttgagaa tgattcctgg ttggtcacgc tgtgaatgca cctgcatctt gtaatatctt 840
 tgatagacta accaactaaa acttaaaacc ttagcagtcg cctgcacaaa cctgaatgca 900
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 gattt 965

<210> 18
 <211> 641
 <212> DNA
 <213> Homo sapiens

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 taattgttta atgcattagc attttttttt acaggggaaca accactgaaa ctgaaatgag 300
 aaagagaagg tcaagttctt tccacgtttc catggacttt ctagaagatc cttcccaaag 360
 gcaacgagca atgagtatag ccagcattct aacaaatata gtagaagggt ggtaacaaat 420
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 ttgtgagttg ggaatagtgc attctaataa aaagacagtc taattcaaga gctgttattt 540
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<210> 19
 <211> 818
 <212> DNA
 <213> Homo sapiens

<400> 19
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<210> 20
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 20
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<210> 21

<211> 829

<212> DNA

<213> Homo sapiens

<400> 21

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caacacagca atatabcagt gcccctgcat tttttatacc aaattctatt ttgtcagtca 720
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<210> 22

<211> 909

<212> DNA

<213> Homo sapiens

<400> 22

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<210> 23

<211> 516

<212> DNA

<213> Homo sapiens

<400> 23

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<210> 24

<211> 640

<212> DNA

<213> Homo sapiens

<400> 24

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 gacaaggaca ttgctaagag atattatgga agcagagaca ctttatctac ttttatttca 180
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 gcttattcat taacacacaa ggatgtgaat attcaattac 640

<210> 25

<211> 607

<212> DNA

<213> Homo sapiens

<400> 25

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ttgcgaggaa aaaaaaaaaaag taacagtaac tactgtttct ctgccctcct attccaatga 180
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ggctggactt cttaattgtt gatgtaggta tcgttcatat tttgtctct gttcaaggta 480
gcttgtctta tttatattca aattctacaa tagtgagtct cagaccacta tgttatgttg 540
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<210> 26

<211> 336

<212> DNA

<213> Homo sapiens

<400> 26

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ttactcagaa cttggagcct atcaatctct caggacacta agagctctga gacctctaag 180
agccttatct cgatttgaag ggatgagggt aagaaaaatg aaagaacctg aagtattgta 240
tatagccaaa attaaactaa attaaattta gaaaaaagga aaaatgtatg catgcaaaag 300
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<210> 27

<211> 677

<212> DNA

<213> Homo sapiens

<400> 27

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aaagaatgga aagaccagag attactaggg gaattttttt tctttattaa cagataagaa 180
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<210> 28

<211> 457

<212> DNA

<213> Homo sapiens

<400> 28

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aaaatatttg ggaaaaagtg tgacaggtaa atattcaagc atagcaatgt ttatcagaaa 420
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<210> 29

<211> 379

<212> DNA

<213> Homo sapiens

<400> 29

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attttcatca tctttgggtc cttcttcacc ttgaacctgt ttattgggtg catcatagat 240
aatttcaacc agcagaaaaa gaagataagt atttctaata ttttctctcc cactgagata 300
gaaaaattat tccttgaggt gttttctctg ccaaagagt acttgaattt agaacaaatg 360
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<210> 30

<211> 393

<212> DNA

<213> Homo sapiens

<400> 30

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tttgattttt cttttctata ctttgagggt caagacatct ttatgacaga agaacagaag 240
aaatactata atgcaatgaa aaaattagga tcgaaaaaac cgcaaaagcc tatacctcga 300
ccaggagtaa gaagtatcaa atgatatggg ggaaaatata aaaacaaaaa ctgcatgctt 360
gtctcacaaa aaagaaaagt aagctaaaca ttt 393

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<210> 31
 <211> 539
 <212> DNA
 <213> Homo sapiens

<400> 31
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<210> 32
 <211> 3403
 <212> DNA
 <213> Homo sapiens

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<210> 33

<211> 8349

<212> DNA

<213> Homo sapiens

<400> 33

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gcttaaactc gtttaaaata tatggttaga gttttctaag aaaatataaa tactgtaaaa 7680
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cttcacaaaa taagaagcaa ggactaggat gcagtgtagg tttctgcttt tttattagta 7860
ctgtaaactt gcacacattt caatgtgaaa caaatctcaa actgagttca atgtttattt 7920
gctttcaata gtaatgcctt atcattgaaa gaggtttaa gaaaaaaa atcagctgat 7980
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atcagatata atatgggatc ccagcttttt ttctctccc acaaaaccag gtagtgaagt 8160
tatattacca gttacagcaa aatactttgt gtttcacaag caacaataaa tgtagattct 8220
ttatactgaa gctattgact tgtagtgtgt tggatgaatg atgcaggaa atgctgttac 8280
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<210> 35

<211> 2005

<212> PRT

<213> Homo sapiens

<400> 35

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Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
 50 55 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
 65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
 85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
 115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
 130 135 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
 145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
 165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
 180 185 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
 195 200 205

Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
 210 215 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
 225 230 235 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val
 245 250 255

Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
 260 265 270
 Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe
 275 280 285
 Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly
 290 295 300
 Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile
 305 310 315 320
 Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu
 325 330 335
 Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile
 340 345 350
 Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp
 355 360 365
 Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp
 370 375 380
 Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr
 385 390 395 400
 Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu
 405 410 415
 Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn
 420 425 430
 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln
 435 440 445
 Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala
 450 455 460
 Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile
 465 470 475 480
 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys
 485 490 495
 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu
 500 505 510

Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser
 515 520 525
 Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
 530 535 540
 Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu
 545 550 555 560
 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser
 565 570 575
 Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp
 580 585 590
 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg
 595 600 605
 Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn
 610 615 620
 Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met
 625 630 635 640
 Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu
 645 650 655
 Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu
 660 665 670
 Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr
 675 680 685
 His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala
 690 695 700
 Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
 705 710 715 720
 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys
 725 730 735
 Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val
 740 745 750
 Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
 755 760 765

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
 770 775 780

Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly
 785 790 795 800

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
 805 810 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser
 820 825 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val
 835 840 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
 850 855 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
 865 870 875 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
 885 890 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
 900 905 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe
 915 920 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
 930 935 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
 945 950 955 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn
 965 970 975

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
 980 985 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
 995 1000 1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe
 1010 1015 1020

Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys
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 Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His
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 Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn
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 Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp
 1075 1080 1085
 Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr
 1090 1095 1100
 Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu
 1105 1110 1115 1120
 Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn
 1125 1130 1135
 Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala
 1140 1145 1150
 Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu
 1155 1160 1165
 Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile
 1170 1175 1180
 Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr
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 Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe
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 Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile
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 Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val
 1235 1240 1245
 Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr
 1250 1255 1260
 Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu
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Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr
 1285 1290 1295
 Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg
 1300 1305 1310
 Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn
 1315 1320 1325
 Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys
 1330 1335 1340
 Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala
 1345 1350 1355 1360
 Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp
 1365 1370 1375
 Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser
 1380 1385 1390
 Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val
 1395 1400 1405
 Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp
 1410 1415 1420
 Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln
 1425 1430 1435 1440
 Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe
 1445 1450 1455
 Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile
 1460 1465 1470
 Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile
 1475 1480 1485
 Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu
 1490 1495 1500
 Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe
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 Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser
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Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr
 1540 1545 1550
 Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu
 1555 1560 1565
 Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser
 1570 1575 1580
 Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val
 1585 1590 1595 1600
 Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu
 1605 1610 1615
 Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg
 1620 1625 1630
 Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr
 1635 1640 1645
 Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly
 1650 1655 1660
 Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser
 1665 1670 1675 1680
 Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn
 1685 1690 1695
 Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr
 1700 1705 1710
 Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro
 1715 1720 1725
 Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly
 1730 1735 1740
 Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile
 1745 1750 1755 1760
 Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu
 1765 1770 1775
 Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu
 1780 1785 1790

Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
 1795 1800 1805
 Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
 1810 1815 1820
 Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
 1825 1830 1835 1840
 Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
 1845 1850 1855
 Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
 1860 1865 1870
 Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
 1875 1880 1885
 Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
 1890 1895 1900
 Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
 1905 1910 1915 1920
 Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
 1925 1930 1935
 Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
 1940 1945 1950
 Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser
 1955 1960 1965
 Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys Glu
 1970 1975 1980
 Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile
 1985 1990 1995 2000
 Arg Glu Ser Lys Lys
 2005

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<212> PRT

<213> Homo sapiens

<400> 36

Met Ala Gln Ser Val Leu Val Pro Pro Gly Pro Asp Ser Phe Arg Phe
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Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
 50 55 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
 65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
 85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
 115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
 130 135 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
 145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
 165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
 180 185 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
 195 200 205

Asn Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
 210 215 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
 225 230 235 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val

245	250	255
Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly		
260	265	270
Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe		
275	280	285
Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly		
290	295	300
Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile		
305	310	315
Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu		
325	330	335
Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile		
340	345	350
Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp		
355	360	365
Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp		
370	375	380
Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr		
385	390	395
Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu		
405	410	415
Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn		
420	425	430
Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln		
435	440	445
Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala		
450	455	460
Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile		
465	470	475
Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys		
485	490	495
Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu		

500	505	510
Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser		
515	520	525
Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser		
530	535	540
Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu		
545	550	555 560
Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser		
565	570	575
Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp		
580	585	590
Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg		
595	600	605
Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn		
610	615	620
Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met		
625	630	635 640
Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu		
645	650	655
Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu		
660	665	670
Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr		
675	680	685
His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala		
690	695	700
Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu		
705	710	715 720
Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys		
725	730	735
Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val		
740	745	750
Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys		

755	760	765	
Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr			
770	775	780	
Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly			
785	790	795	800
Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr			
	805	810	815
Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser			
	820	825	830
Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val			
	835	840	845
Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp			
	850	855	860
Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala			
865	870	875	880
Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala			
	885	890	895
Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys			
	900	905	910
Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe			
	915	920	925
Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile			
	930	935	940
Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu			
945	950	955	960
Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn			
	965	970	975
Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala			
	980	985	990
Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly			
	995	1000	1005
Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe			

1010	1015	1020
Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys		
1025	1030	1035 1040
Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His		
	1045	1050 1055
Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn		
	1060	1065 1070
Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp		
	1075	1080 1085
Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr		
	1090	1095 1100
Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu		
	1105	1110 1115 1120
Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn		
	1125	1130 1135
Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala		
	1140	1145 1150
Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu		
	1155	1160 1165
Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile		
	1170	1175 1180
Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr		
	1185	1190 1195 1200
Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe		
	1205	1210 1215
Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile		
	1220	1225 1230
Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val		
	1235	1240 1245
Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr		
	1250	1255 1260
Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu		

1265	1270	1275	1280
Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr	1285	1290	1295
Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg	1300	1305	1310
Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn	1315	1320	1325
Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys	1330	1335	1340
Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala	1345	1350	1355
Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp	1365	1370	1375
Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser	1380	1385	1390
Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val	1395	1400	1405
Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp	1410	1415	1420
Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln	1425	1430	1435
Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe	1445	1450	1455
Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile	1460	1465	1470
Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile	1475	1480	1485
Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu	1490	1495	1500
Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe	1505	1510	1515
Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser			

	1525		1530		1535
Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr					
	1540		1545		1550
Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu					
	1555		1560		1565
Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser					
	1570		1575		1580
Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val					
	1585		1590		1595
					1600
Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu					
	1605		1610		1615
Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg					
	1620		1625		1630
Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr					
	1635		1640		1645
Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly					
	1650		1655		1660
Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser					
	1665		1670		1675
					1680
Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn					
	1685		1690		1695
Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr					
	1700		1705		1710
Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro					
	1715		1720		1725
Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly					
	1730		1735		1740
Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile					
	1745		1750		1755
					1760
Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu					
	1765		1770		1775
Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu					

1780	1785	1790
Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp		
1795	1800	1805
Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala		
1810	1815	1820
Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile		
1825	1830	1835 1840
Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp		
1845	1850	1855
Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met		
1860	1865	1870
Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro		
1875	1880	1885
Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln		
1890	1895	1900
Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu		
1905	1910	1915 1920
Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys		
1925	1930	1935
Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp		
1940	1945	1950
Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser		
1955	1960	1965
Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys Glu		
1970	1975	1980
Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile		
1985	1990	1995 2000
Arg Glu Ser Lys Lys		
2005		

<210> 37
 <211> 912
 <212> DNA

<213> Homo sapiens

<400> 37

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gaattcttta tatgggttga atgactttct gacatagcaa ataaaaagca tgaggagaag 60
cattatctgt taacaaaatt aacacttaaa atcaacaaag ttttaatgtt tcgttccaag 120
aaaagcctgt ggaagatcag ttccacaact gagagctttg ggctgcttca gacatatgtc 180
tgtgtgtacg ctgtgaaggt gtttctcttc acagttcccc gccctctagt ggtagttaca 240
ataatgccat tttgtagtcc ctgtacagga aatgcctctt cttacttcag ttaccagaat 300
ccttttacag gaagttaggt gtggtctttg aaggagaatt aaaaaaaaaa aaaaaaaaaa 360
aaaaaagatt tttttttttt taaagcatga tggaaattta gctgcagtct tcttggggcc 420
agcttatcaa tcccaaactc tgggggtaaa agattctaca ggggtaatgt tttattattc 480
ttattatgct tattctctgt gatgcttctc tacctttaca gtagtagaat ccttggggaa 540
atctgcagag ggaccacttt cattttgaag ctgctggctg catgttttag catgtctctt 600
ctattagaga atccaggcat ggcagtttcc tccccagtg tgcaaggacc atcttcatgc 660
ctatgtctgt cgctaggcat gagggctctc aggaatgggt gaaaaaaatg agggatgttt 720
tggaggcact ataatactgg ggagggcagt ctgctagctg gtagctgaaa ggtcctggtt 780
tacttcaaca ttttttttaa ataaaactgt gcagtagttt ttgttatttt agggttccct 840
ctgttttatc tgggtgatgc tgcagaagtg aactgcataa cacatttcac tcttagaaat 900
gcattccata ta 912

```

<210> 38

<211> 722

<212> DNA

<213> Homo sapiens

<400> 38

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ctcagtgcac gtaactgaca caatcacctc tatctaattg tcatgcttct tacctcctgt 60
tctgtagcac tttcttatgc aaggagctaa acagtgatta aaggagcagg atgaaaagat 120
ggcacagtca gtgctggtac cgccaggacc tgacagcttc cgcttcttta ccagggaatc 180
ccttgctgct attgaacaac gcattgcaga agagaaagct aagagaccca aacaggaacg 240
caaggatgag gatgatgaaa atggcccaaa gccaaacagt gacttggaag cagsaaaatc 300
tcttccattht atttatggag acattcctcc agagatggtg tcagtgcccc tggaggatct 360
ggacccctac tatatcaata agaaagtgag ttcttagtca agttgccttc actgcctatt 420
tactaattgg ttctgggcta gtcccaggga tgatggtgaa gaaggctggc ctccttcctt 480
ctgtctaaag tatcactaag atgctggatg ggcctgaccg tgtaatggac caatgatcct 540
agaagtcttt tggaagcact catthgaacc tgcatttgtg agacaggcag agaactggtg 600
aggcatcctc cagcgcgga attaaggaag gacaaaagcc tattcacctt cttgaatata 660
aattatatgc ttaaaccagt gtaaattgac cctgattccc taataatgtt gagaagcaaa 720
aa 722

```

<210> 39

<211> 561

<212> DNA

<213> Homo sapiens

<400> 39

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cctatggcat tgatcacaaa ttttcttaat aatcctcatg tcatttatca aatttaggaa 60...
agtttatagt gctcagaaaa aaaaagcatc tatcttcatg tcatatgatg gtaattatta 120
tgttatacac tattttacag ggcaatattt ataaataatg gttttacttt tctcttaaaa 180
tattcttaat atatatctta agttttggtt tatgtgttgt gttttctttt tcagacgttt 240
atagtattga ataaagggaa agcaatctct cgattcagtg ccacccctgc cctttacatt 300
ttaactccct tcaaccctat tagaaaatta gctattaaga ttttggtaca ttcataatcct 360
ttttcaaatc gtcacttaat atgattttct tctttgacca agttattgag ctacacattt 420
tccaaaatat ctgtggttgg caatgttatg tgttctttct ttttctttcc ttttactcaa 480
tcgttagcat gttgcaaaat gagatcacag gtaagtgaat tactttcccc cgtcttctaa 540
gtgtttcttc tctacccaac t                                     561

```

<210> 40

<211> 510

<212> DNA

<213> Homo sapiens

<400> 40

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acctaaatag cctcaaaaata gttgatggct tggcctgaag acaagatcta aatatgaggt 60
tgctgagtta tagaaatggc aaaaaaaagg gtcaataata gaataataag caacaaaata 120
atagtaagca ctaaagtttt aaacttcatg gtggtgaagg catggtagtg cataaaagta 180
agatttttcc attgaacttt gtcttccttg acgatattct actttattca atatgctcat 240
tatgtgcacg attcttacca actgtgtatt tatgaccatg agtaaccctc cagactggac 300
aaagaatgtg gagtaagtat aaatatTTTT caatattgac ctccctttat gtttcatatt 360
gtgcttttaa caccttgaga cctcctcaat ttctttaaca aatcatgcta gctactgtta 420
accagaccct gattcaaat catttctgtc actaaatgtc ttctaggaca aagcttgtag 480
tgggctcact tagttgtgta aattactgca                                     510

```

<210> 41

<211> 370

<212> DNA

<213> Homo sapiens

<400> 41

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taagatatgt acttgtaaata taaccactag atttttaatg tgagcttggc tattgtctct 60
caggatatacc tttacaggaa tttatacttt tgaatcactt attaaaatac ttgcaagggg 120
cttttgttta gaagatttca catttttacg ggatccatgg aattggttgg atttcacagt 180
cattactttt gcgtaagtat cttaatacat tttctatcct ggaagagtaa atcactggtg 240
ggagcctata ctatattttc cttggtggct tgccttgaca gaccaagcat ttntcttagt 300
aatcatagtt ttcttccaat caaattatcc agtttggaga aattaggaac tatcatagta 360
aattacatgg                                     370

```

<210> 42

<211> 370

<212> DNA

<213> Homo sapiens

<400> 42

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caattagcac tgtaaagtaa taaagtttcc caaataacag agattatgat tgatgacaat 60
gccattttcc tcttaattgg gaaagctgat ggcgacactc atgaaattaa aaaggtcttg 120
atgaaagacc aangaagacg tagatttccc taaattctga ataactctga ttttaattcta 180
caggatgtga acagaatttg taaacctagg caatgtttca gctcttcgaa ctttcagagt 240
cttgagagct ttgaaaacta tttctgtaat tccaggtaag aagaaaatgg tataagggtg 300
taggccctt atactctcaa ctgtttcttg tgttctgtca ttgtgtttgt gtgtgaaccc 360
cctattacag                                     370

```

<210> 43

<211> 410

<212> DNA

<213> Homo sapiens

<400> 43

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gtaagaagaa aatggtataa ggtggttagc cccttatatc tccaactgtt tcttgtgttc 60
tgtcattgtg tttgtgtgtg aaccccctat tacagatatg tgacagagtt tgtggacctg 120
ggcaatgtct cagcggttag aacattcaga gtctccgag cattgaaaac aatttcagtc 180
attccagggt agagctaggt taaacaccga ggctgacttt agctacagtg gtgtacaat 240
cacagctttt gtgcagaagc cttgttgcta gttgcatatt gcaaataaat atgtaaaaaa 300
gcaagaattg gtacatcatt ttttgatgg atttgattct ttgcttttta cccgttgctt 360
tctttaaaac tattctaaat cagccttga gtttaacaag tgttgcata 410

```

<210> 44

<211> 1066

<212> DNA

<213> Homo sapiens

<400> 44

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aaagagtgtt tggaaataca catttggttc atttccattc acagttttct aatgaacata 60
caagttctgc tttcattcat tttcaccagc tagtaggctt ttcataaaaa tgttattcaa 120
tcacaaacat taaactaata ttgttggcat tctgcatgac atttttattt tccaggccaa 180
gctcatgata tttttgccgg taaaatagct gttgagtagt atatttaant tcccccttct 240
gattttgttt gtaggcctga agaccattgt gggggccctg atccagtcag tgaagaagct 300
ttctgatgtc atgatcttga ctgtgttctg tctaagcgtg tttgcgctaa taggattgca 360
gttgttcatg ggcaacctac gaaataaatg ttgcaatgg cctccagata attcttcctt 420
tgaaataaat atcacttccct tctttaacaa ttcattggat gggaaatgga ctactttcaa 480
taggacagtg agcatattta actgggatga atattattgag gataaaaagta agatatactc 540
tataaaccat taagttgttt agttctctaa atattaaata ttatatataa tggaaattat 600
ctcaatttag atgtgaatca agtgacttag actaatttaa gatgatttaa tacatataaa 660
agagatatca aaggatacct tattctattt ttsttatctg tccattgata tagtaaaagt 720
tctcatttga aaatgtgttg tcttatactc atgttgaaag taatttcata ttatgccata 780
ttaaaaaagg tttatttggt agacattaat cagggttttc agtcatttta ataaataagt 840
cagtagtttg aactattcmg cgtattccac tgaaatgtcg ttaagaagac tgaggggaaa 900
taatttggcc ctatttggtt gatgcaacat atgtattgag tacatatgct atacttgaaa 960

```

ctagagaaac catttatcaa gatgaaataa gaatttgtgt gctcctcaga aggttaagta 1020
 accctgattt agccattcac ttcattcata ttctaattag tccctt 1066

<210> 45

<211> 385

<212> DNA

<213> Homo sapiens

<400> 45

gttcaattat tgtgaaaaat cttcttttagc catatatatt tattagttta tccatctcat 60
 tatgattgaa aacatttgtg agctttgcca cctaaacagg gtggctgaag tgttttacag 120
 gattttaatg attctttcta ttcccttctc tttaaataagg tcacttttat tttttacagg 180
 ggcaaaatga tgctctgctt tgtggcaaca gctcagatgc agggtaagtg tatgcttcc 240
 actgagtttc agtccacact gctccatcag tgtcaataac ctgccacctc ccaactcatcc 300
 agtcccacca ctctcactc aaaaccctcc ataaattcta cttcacgggtg actctcagaa 360
 tgaccaggat aagtgtagat tctca 385

<210> 46

<211> 430

<212> DNA

<213> Homo sapiens

<400> 46

tataataatg acaattatga atcacagagg aatccacaaa gtagacctta tagattctgt 60
 cattatataa atcagtcacac ttagtgctga gttaagtact gggtaagggtg agagaaatcg 120
 gcttttttct agtgctgtga taaaacagac attggcatat attaaaacag gaaaaccaat 180
 tagcagactt gccgttattg actycctctc tttcctctaa cctaattaca gccagtgtcc 240
 tgaaggatac atctgtgtga aggctggtag aaaccccaac tatggctaca cgagctttga 300
 cacctttagt tgggcctttt tgctcttatt tctgtctcatg actcaagact tctgggaaaa 360
 cctttatcaa ctggtgagaa cagataaaat ctttttctg agaatcataa aacaccgaac 420
 tcaagagaat 430

<210> 47

<211> 646

<212> DNA

<213> Homo sapiens

<400> 47

tgctgtagaa tattttatta cttagagtgt aagtttgtaa catcctatat aaaatttatt 60
 aaaatctctc ttccattttg cagacactac gtgctgctgg gaaaacgtac atgatatttt 120
 ttgtgctggc cattttcttg ggctcattct atctaataaa tttgatcttg gctgtggtgg 180
 ccatggccta tgaggaacag aatcaggcca cattggaaga ggctgaacag aaggaagctg 240
 aatttcagca gatgctcgaa cagttgaaaa agcaacaaga agaagctcag gtatagttaa 300
 caagcatacg gtcctttgtt tttctgtatc taaattcttt aacctaaatg ttgaggtcag 360
 tggcaaggta gttgacatta gaaataggct atatgtgttt ggtaagtgtc aggagcctgt 420

```

ttggttatta agaagttatt actttattgc aatgatctct gtcaatagtg tcaatagtaa 480.
tggcatcaaa aaatggataa ttataattgc ttactgaca tttttttctc ctttgtgact 540
ccttgaggaa attaatgatt aacaaaggcc tcatgtactc aaacttgcag agtagataaa 600
cctacatgtc ctcagttgaa gtattttctt aggggaagag gaattc 646

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<210> 48

<211> 711

<212> DNA

<213> Homo sapiens

<400> 48

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tatgtatcat cttccatatt aatgcgcatt ttactctttg attgggtctaa taacagtgtg 60
ctgtgttcta aaacacagaa taaaatggag aattgttttt caagattatc ttcattgatat 120
tgaagctcaa ttaagcagta acatgataat ttttttttaa gatnatatgc aacttcccac 180
atactttgcg cccttctagg cggcagctgc agccgcattc gctgaatcaa gagacttcag 240
tgggtgctggt gggataggag ttttttcaga gagttcttca gtagcatcta agttgagctc 300
caaaagttaa aaagagctga aaaacagaag aaagaaaaag aaacagaaaag aacagtctgg 360
agaagaagag aaaaatgaca gagtctctaa atcggaatct gaagacagca taagaagaaa 420
aggtttccgt ttttcttgg aaggaagtag gctgacatat gaaaagagat tttcttctcc 480
acaccaggta aaaatattaa attacatgaa ttgtgttctc ataaattttt taaaagaata 540
tgccagaatt taatggagag aaaaccgcct tccacctgga tggcacaatg ctttcagagt 600
agtgatgatt atcaagtgtt ttggctatca cttcagagaa tttgtgagtt ttgcaacttt 660
ttggaatccc aggaaggaaa ttttagatcc ctctgggttt ggaaaaattt g 711

```

<210> 49

<211> 1026

<212> DNA

<213> Homo sapiens

<400> 49

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ttatggggac acttctgact atgttgaggt gtgggtaaag taggagaaaa gagagcagaa 60
gatggaaaat ggaggaagga gaaaaagcga gagtgaata gaaaagggtga acctgttaga 120
aagtgccaaa atgccaccag cagtcattcag aggggtgctt tcttccacat gtccaatgac 180
ttatccttga gtaagtcaat gactatgaca caatgaatca aattctgttt ttcagaatgc 240
cagctcttaa ctctcttcat ctcatTTTTTg tttcttttct tgttattcat agtccttact 300
gagcatccgt ggctcccttt tctctccaag acgcaacagt agggcgagcc ttttcagctt 360
cagaggtcga gcaaaggaca ttggctctga gaatgacttt gctgatgatg agcacagcac 420
ctttgaggac aatgacagcc gaagagactc tctgttcgtg ccgcacagac atggagaacg 480
gcgccacagc aatgtcagcc aggccagccg tgcctccagg gtgctcccca tcttgcccat 540
gaatgggaag atgcatagcg ctgtggactg caatggtgtg gtctccctgg tcggggggccc 600
ttctaccctc acatctgctg ggcagctcct accagaggtg aggccaaacy magattgcag 660
ctgatgtgaa gagagttgtg actggtgcag gcaggagtgy ttttccattt mcacatctaa 720
gaatttkttg agtttsttgc ccaaaggctg ggagtttgtt caatcaagct gttaactgtc 780
ttgtgaaact sttctattca gacttctycta caaagtaatt aaaaacctag gttggctgtc 840
agagaatata attagamgtm atctttcattc ayyattacta tggatatgaaa ctgcgcaaaa 900
agcaaagcaa caatttatca agcataatgt tygaytaata tagttaaatt aaatccaag 960

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aaattaatgc tcacaaatta aataaatact taaggatttt gtgattgttg ttcatttaaa 1020
aggaga 1026

<210> 50

<211> 601

<212> DNA

<213> Homo sapiens

<400> 50

ataggaaagc ccaccttgac aaacccaggg ctccccaaaa gctgaaaatc tgacagactt 60
taaacaaccc ccaaataatt atcattccaa caatatctta gtgagctttt tacatctgag 120
aaagcatggt gtatatcttag ttaaataaca cctgttgtag gaatgctttg ggctttgctg 180
ctttcaaaaa tagtggttat ttcactctgaa attctacttc tagggcacia ctactgaaac 240
agaaataaga aagagacggg ccagttctta tcatgtttcc atggatttat tggaagatcc 300
tacatcaagg caaagagcaa tgagtatagc cagtattttg accaacacca tggaaggatc 360
gttaaaagtc ctgcgtcaca gttacttggt gctttcctaa tgatgaaaaa cacttcataa 420
atttcaataa aatacttcct gacttgatat tgtatcatta ttacacattt tactaaataa 480
cagtaaaatc cgtgcataac tcatggattc atatattcca cagatttttt ttttttatat 540
ttagcctgta gaaagctgct gcaaatgtaa ggtatatttg aacaccactt tcataactta 600
a 601

<210> 51

<211> 645

<212> DNA

<213> Homo sapiens

<400> 51

gcttactagc ctttctgtac tgatcctttc tatgacagca aaccatttgt aaaattttcc 60
ctgttcctcc agcagattaa ccataatat cttttaacaa ctttagattt tttaaattcc 120
ttttaattta aaccaaattc gcttaataga aagtaagcag tttcatgag gattctaact 180
ttttttcttc cagaacttga agaattccaga cagaaatgcc caccatgctg gtataaattt 240
gctaataatg gtttgatttg ggactgttgt aaaccatggt taaagggtgaa acaccttgct 300
aacctgggtg taatggaccc atttggtgac ctggccatca ccatctgcat tgtcttaaat 360
acactcttca tggctatgga gcactatccc atgacggagc agttcagcag tgtactgtct 420
gttggaacc tggttaagcct cactgagagt ttctcttcc cttgaaagag tttataattg 480
ccttagtgaa ttttacatat tgctctcaaa ttaaataatca actaattggc catgtatatc 540
ttgacatcaa atgttttagca tcccttttaa ataacaaaaa aatgttgcta ccatagtgca 600
aaagagtcaa agaatttatg tacaatttga tttagaattg aattt 645

<210> 52

<211> 485

<212> DNA

<213> Homo sapiens

<400> 52


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tggcccaaac caatttttaa atcaggaatt taattttwtat attgttggga gttaaattaa 60...
gttgctcaat aattattcgt gtttcaakas tatttgctca tataatgaac tacacttctc 120
atntaggtct tcacagggat cttcacagca gaaatgtttc tcaagataat tgccatggat 180
ccatattatt actttcaaga aggttggaat atttttgatg gttttattgt gaggccttagt 240
ttaatggaac ttggtttggc aaatgtggaa ggattgtcag ttctccgatc attccggctg 300
gtaaattaac tgggagtgtt cataaaatgt acttttrtaat taattagtct tcattctcat 360
ctagtaaaaa tggcaagatt tcccatcatt ataatatatt tgaatacctt ctaaaacaga 420
ttggattgcc ataccaccaa atggtagttt cttcttcac atagctttaa taaagttcac 480
ttaaa                                           485

```

<210> 53

<211> 602

<212> DNA

<213> Homo sapiens

<400> 53

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acagatttcc tcctgtgtcc atgtgactaa cccattgtgc acatgtaccc taaaaattag 60
tatataataa taaaataaaa taaaaataaa aataaaaaaa taaaaataaa ataaaattgc 120
agattttttt agaaatgcag agattaacac tgttcttgct tttatttcca gctccgagtt 180
ttcaagttgg caaaatcttg gccaaactcta aatatgctaa ttaagatcat tggcaattct 240
gtgggggctc taggaaacct caccttggtg ttggccatca tcgtcttcat ttttgctgtg 300
gtcggcatgc agctcttttg taagagctac aaagaatgtg tctgcaagat ttccaatgat 360
tgtgaactcc cacgctggca catgcatgac tttttccact ccttcctgat cgtgttccgc 420
gtgctgtgtg gagagtggat agagaccatg tgggactgta tggaggtcgc tggccaaacc 480
atgtgcctta ctgtcttcat gatggtcatg gtgattggaa atctagtggg atgtagcaaa 540
aacattttcc tcattttcat taaaaataat gtaatcatta aaaagtgttc aactgaagaa 600
ta                                           602

```

<210> 54

<211> 803

<212> DNA

<213> Homo sapiens

<400> 54

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gtttcattta gcaatgattt cagtattttc tgcaatgact aataagcaaa tagtgataat 60
agtattattt tatattgacc aagcattttt atttcattca ctttttttca gaatagtgtg 120
tcatgaatta gcagaaatgc atgttagaat aaaataaggt gtcaagaaca atcttagaaa 180
actaatgatg gaaagcaatt gaagcaatag aatgttttga tcacctgttt ttctgtgtgt 240
gtttcaggtt ctgaacctct tcttggcctt gcttttgagt tccttcagtt ctgacaatct 300
tgctgccact gatgatgata acgaaatgaa taatctccag attgctgtgg gaaggatgca 360
gaaaggaatc gattttgtta aaagaaaaat acgtgaattt attcagaaag cctttgttag 420
gaagcagaaa gcttttagatg aaattaaacc gcttgaagat ctaaataata aaaaagacag 480
ctgtatttcc aaccatacca ccatagaaat aggcaaaagac ctcaattatc tcaaagacgg 540
aatggaact actagtggca taggcagcag tgtagaaaaa tatgtcgtgg atgaaagtga 600
ttacatgtca ttataaaaca accctagcct cactgtgaca gtaccaattg ctgttgaga 660
atctgacttt gaaaatttaa atactgaaga attcagcagc gagttagata tggaggaaag 720

```

caaagaggta aaatgttaaa taaggagata ttttgggtgta tataatctgt gttaaataatc 780
 aggtgtttta tgcgtgtctc tgt 803

<210> 55

<211> 615

<212> DNA

<213> Homo sapiens

<400> 55

atctctatac taggtcctaaa cagaagttat ttccgttggt agcaccatat ttttaaaaga 60
 aaaaaaaata ctatgggtgt gtatctaata ttgtgacccc tgacctttac caaagcggat 120
 tggcattatg ttttaagttct taattacaga tcaagaaaaa tgcatacaga agatgggggg 180
 gggcacacct aattaatttt tatatttaga ttaaagaaaa taattaaatg tggttttttg 240
 tgggattgat tttcagaagc taaatgcaac tagttcatct gaaggcagca cggttgatat 300
 tggagctccc gccgagggag aacagcctga gggtgaacct gaggaatccc ttgaacctga 360
 agcctgtttt acagaagnnn nnnnnnaagc aaaacaataa catatgtggt cttgagtatc 420
 ctcttttcta cccatttttt cctatttatt taaatgtctg tttatttgtc taccatctag 480
 ttcatctatc tatctgtatc tatctatcta tctatctatc tagtaatcat ctatacctat 540
 ccaacaactg tacatttatt tggttttttt ttttgcattt gctgtttgaa aaaaaatgca 600
 acgttttaaa ggcaa 615

<210> 56

<211> 400

<212> DNA

<213> Homo sapiens

<400> 56

gatagctttt gtaagcggaa gctatcttaa aaattaatgt tatttacaat gtattatcag 60
 gtaataatgt aaatgaatct cccaccaaca caaatatacc taatcaaaga gtaatttttt 120
 gtcttcattt ttttccaca tatttttagac tgtgtacgga agttcaagtg ttgtcagata 180
 agcatagaag aaggcaaagg gaaactctgg tgggaatttga ggaaaacatg ctataagata 240
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<210> 57

<211> 560

<212> DNA

<213> Homo sapiens

<400> 57

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<210> 58

<211> 480

<212> DNA

<213> Homo sapiens

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<210> 59

<211> 640

<212> DNA

<213> Homo sapiens

<400> 59

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<210> 60

<211> 480

<212> DNA

<213> Homo sapiens

<400> 60

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<210> 61

<211> 366

<212> DNA

<213> Homo sapiens

<400> 61

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<210> 62

<211> 560

<212> DNA

<213> Homo sapiens

<400> 62

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<210> 63

<211> 650

<212> DNA

<213> Homo sapiens

<400> 63

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<211> 3700

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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 Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
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Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
 370 375 380
 Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
 385 390 395 400
 Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
 405 410 415
 Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
 420 425 430
 Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
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 Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
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 Ala Ser Ala Ala Ser Arg Asp Phe Ser Gly Ile Gly Gly Leu Gly Glu
 465 470 475 480
 Leu Leu Glu Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala
 485 490 495
 Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
 500 505 510
 Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
 515 520 525
 Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
 530 535 540
 Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
 545 550 555 560
 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
 565 570 575
 Ile Phe Ser Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp
 580 585 590
 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Ser Glu Ser Arg Arg
 595 600 605
 Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
 610 615 620

Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
 625 630 635 640
 Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
 645 650 655
 Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
 660 665 670
 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
 675 680 685
 Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
 690 695 700
 Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
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 Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
 725 730 735
 Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
 740 745 750
 Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
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 Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
 770 775 780
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 Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
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 Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
 835 840 845
 Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
 850 855 860
 Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
 865 870 875 880

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
 885 890 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
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Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
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Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
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Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
 945 950 955 960

Arg Met Gln Lys Gly Ile Asp Tyr Val Lys Asn Lys Met Arg Glu Cys
 965 970 975

Phe Gln Lys Ala Phe Phe Arg Lys Pro Lys Val Ile Glu Ile His Glu
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Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile
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Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly
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Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp
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Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile
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Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser
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Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser
 1075 1080 1085

Ser Ser Glu Gly Ser Thr Val Asp Val Val Leu Pro Arg Glu Gly Glu
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 Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr
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 Thr Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp
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 Tyr His Cys Val Asn Met Thr Thr Gly Asn Met Phe Asp Ile Ser Asp
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 Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
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 Ala Val Asp Ser Arg Asp Val Lys Leu Gln Pro Val Tyr Glu Glu Asn
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Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
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Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
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Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
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Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
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Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
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Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
 1475 1480 1485

Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
 1490 1495 1500

Met Thr Leu Val Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
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Thr Gly Glu Phe Val Leu Lys Leu Val Ser Leu Arg His Tyr Tyr Phe
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Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
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Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
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Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
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Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
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Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
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Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
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Lys Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
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Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
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Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
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Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
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Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
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Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
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Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
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Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
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Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
 1795 1800 1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
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Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
 1825 1830 1835 1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
 1845 1850 1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
 1860 1865 1870

Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
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Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
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Thr Pro Glu Lys Thr Asp Gly Ser Ser Ser Thr Thr Ser Pro Pro Ser
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<211> 1951

<212> PRT

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Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
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Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
 65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Met Asn Lys Gly
 85 90 95

Lys Ala Ile Ser Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
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Pro Leu Asn Pro Val Arg Lys Ile Ala Xaa Lys Ile Leu Val His Ser
 115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
 130 135 140

Met Thr Leu Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
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Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala Arg
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Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
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Leu Asp Phe Ser Val Ile Val Met Ala Tyr Val Thr Glu Phe Val Ser
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Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
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Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
 225 230 235 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
 245 250 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
 260 265 270

Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Ser Asp Ser Ala Phe Glu
 275 280 285

Thr Asn Thr Thr Ser Tyr Phe Asn Gly Thr Met Asp Ser Asn Gly Thr
 290 295 300

Phe Val Asn Val Thr Met Ser Thr Phe Asn Trp Lys Asp Tyr Ile Gly
 305 310 315 320

Asp Asp Ser His Phe Tyr Val Leu Asp Gly Gln Lys Asp Pro Leu Leu
 325 330 335

Cys Gly Asn Gly Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile Cys
 340 345 350

Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
 355 360 365

Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
 370 375 380

Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
 385 390 395 400

Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
 405 410 415

Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
 420 425 430

Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
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 Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
 450 455 460
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 465 470 475 480
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 485 490 495
 Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
 500 505 510
 Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
 515 520 525
 Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
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 Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
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 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
 565 570 575
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 580 585 590
 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Ser Glu Ser Arg Arg
 595 600 605
 Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
 610 615 620
 Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
 625 630 635 640
 Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
 645 650 655
 Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
 660 665 670
 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
 675 680 685

Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
 690 695 700

Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
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Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
 725 730 735

Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
 740 745 750

Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
 755 760 765

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
 770 775 780

Leu Ser Leu Met Glu Leu Gly Leu Ser Asn Val Glu Gly Leu Ser Val
 785 790 795 800

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
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Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
 820 825 830

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
 835 840 845

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
 850 855 860

Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
 865 870 875 880

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
 885 890 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
 900 905 910

Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
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	980	985	990
Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile			
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Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly			
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Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp			
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Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile			
	1045	1050	1055
Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser			
	1060	1065	1070
Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser			
	1075	1080	1085
Ser Ser Glu Gly Ser Thr Val Asp Val Val Leu Pro Arg Glu Gly Glu			
	1090	1095	1100
Gln Ala Glu Thr Glu Pro Glu Glu Asp Leu Lys Pro Glu Ala Cys Phe			
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Thr Glu Gly Cys Ile Lys Lys Phe Pro Phe Cys Gln Val Ser Thr Glu			
	1125	1130	1135
Glu Gly Lys Gly Lys Ile Trp Trp Asn Leu Arg Lys Thr Cys Tyr Ser			
	1140	1145	1150
Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu			
	1155	1160	1165
Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu Gln Arg			
	1170	1175	1180
Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr			
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 Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe
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 Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
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Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
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 Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
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 Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
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 Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
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 1665 1670 1675 1680
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 Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
 1860 1865 1870
 Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
 1875 1880 1885
 Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
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<211> 1380

<212> DNA

<213> Homo sapiens

<400> 69

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atacatacag ggagacatag cacagatgac cttagggaat ggaatgatgc caaaggctgt 720

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tgatgtaaga aagagagatt aactcagttt tttttttgtt tttgtttttt tgttgttgtt 780.
gttgttgttt tgagacagag tctctctctg tcgcccaggc tggagtgcag tggcatgaac 840

<210> 71

<211> 780

<212> DNA

<213> Homo sapiens

<400> 71

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ataaaattat gtaagaactc tgtataataa gctcacagag tacaagaaag gagaggaaaa 180
aagtataaga gaactgcgaa agaactatga gggatttcca aacagcaaaa ttgtcattga 240
agccatgaga aactctactc actaaattct ttaatttctc agcctaccca aatattgggc 300
aaaccctaatt tctcttgagc gggaaaagct gagagtctgg aactagccta tcttccgagg 360
acttagagac aacagtatgg gaatttcaac gagacgtttt tactttcttt tgaccaagat 420
tcaaattctt tattccagcc cttgataagt aaataagaag gtaaaggact atttatttgt 480
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ataattttgtg aaaattactc ggtgatttcc acattagata ttttaaacct aatgttattt 600
ctaaaacaaa aaccaaccag gagaatccaa ttaagtaaaa tgatgtgatt aatataaatt 660
agctattccc atctggaaaa gggcagccat ttctgtgttg aggtgcctca atgatactga 720
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<210> 72

<211> 1025

<212> DNA

<213> Homo sapiens

<400> 72

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agaatttttt aaatgctttt aaaaaatgga caaaattata gatattcttg agtttaataa 180
taatgtttat atattatata tactgtacat tgtagaatgg cttaatcaaa ctaattaaca 240
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gatgttttca agttcaaatg ttagtgagcag tactaaaagc atgacttaat gtttatagct 360
ttaaaaagtt actaaagaat gacatttttg ttgatgttct tatgccaat cgcttgcttt 420
cctaactctt gtgcaatttt tctttttatt gcaggtaatt cgtatgcaag aagctacacg 480
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agcttccgcc tttttactag agaattctct gctgctatcg aaaaacgtgc tgcagaagag 600
aaagccaaga agcccaaaaa ggaacaagat aatgatgatg agaacaaacc aaagccaaat 660
agtgacttgg aagctggaaa gaaccttcca tttatttatg gagacattcc tccagagatg 720
gtgtcagagc ccctggagga cctggatccc tactatatca ataagaaagt gattattgat 780
tttagacttc taataaatct ttaatgaaac tcttaactgt aatatacttt tctgggcctt 840
atatacagca tcacaatttt tcttctgtta aagattttat aatactcttc actgtcactt 900
atttttatca caatataata aaacaaacat ttataagaaa tgaagtcaag agttgggttac 960
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caaaa

1025

<210> 73

<211> 433

<212> DNA

<213> Homo sapiens

<400> 73

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ctccttaaat aagcccatgt ctaatttagt aattttactc gtattttctg tttcagactt 180
ttatagtaat gaataaagga aaggcaattt cccgattcag tgccacctct gccttgata 240
ttttaactcc actaaaccct gttaggaaaa ttgctabsaa gattttggta cattcatatc 300
cttttaatgt gaattgccta aatgctattt ctaacagttg attttaaaaga aaatgtcagt 360
tatattttca agtatctgta aaatttcttt gagattaatg gtaacattgt tagtttaatt 420
catttatttg cat 433

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<210> 74

<211> 450

<212> DNA

<213> Homo sapiens

<400> 74

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gagtgcacca aggccatatt acaggctttg aagtttctta ttattttatc attgttttaa 60
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atttataaat ggccatggta acctactaac atttattcct taactataat ctactttatt 180
cagcatgctt atcatgtgca ctattttgac caactgtgta tttatgacct tgagcaaccc 240
tcctgactgg acaaagaatg tagagtaagt aggaataact tctgggaatg agaaatgcac 300
actcaaatc tctagcaatc tccttgaggg tatagcctga cttatggttt ccacttctgt 360
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cttctacgag gtaagtattt tcccacaaaa 450

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<210> 75

<211> 701

<212> DNA

<213> Homo sapiens

<400> 75

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aaaatttacc atttgyggct ttccattaca tttctatcag ataactctgc gctagtaggt 60
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accagattag attcctaaag aatataattt ctcttcagtt taactctttg ctcaggcttg 180
taaaactaac taaatgaata gattatttgg taaatagaag taaggacaa tattttaatg 240
aatgaaaaa ccacaaaagg ataggatttg ctatgattga aaacatttat tttacagtt 300
caagcaaat tgtaatttt ggcttggatg ttttcttag gtacacattc actggaatct 360
atacctttga gtcacttata aaaatcttgg caagagggtt ttgcttagaa gattttacgt 420

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ttcttcgtga tccatggaac tggctggatt tcagtgtcat tgtgatggcg tgagtaactt 480.
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 catatattaa atgtagagct ttcttgtag tcaagttaac tatatgggtt gtgtattttc 600
 agaatacata ttagaataca tattgcaatg taaatatatc cagtaaataga tcaataaatg 660
 gggttatctt catgtcatat agtctttctc ttcataaaaa t 701

<210> 76

<211> 286

<212> DNA

<213> Homo sapiens

<400> 76

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 aagcctaggc aatgtttcag cccttcgaac ttccagagtc ttgagagctc tgaaaactat 180
 ttctgtaatc ccaggtaga agaaactggg gtaaggtagt aggccoctta tatctccaac 240
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<210> 77

<211> 515

<212> DNA

<213> Homo sapiens

<400> 77

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 aatgtctcag cggtgagaac attcagagtt ctccgagcac tgaaaacaat ttcagtcatt 180
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 ccaaatgatg tttcaatgtc agtttagctc ctaaaatttt ataaattaca tgcgtattta 360
 taaagtcagc ctttgagttt aacagaaaat tgcatgagac atcttcaaaa aatgctaatt 420
 tgggcctctt gcgctctctc tctctctttt tcaactaccat ggctttacta acagatttgg 480
 attttaccat tcgctgcaga tgtagttcaa aaatg 515

<210> 78

<211> 564

<212> DNA

<213> Homo sapiens

<400> 78

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 atgatttctg gcactcttcc tcaggttaacc tatagttctc tctctgcagg tttaaagacc 240
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 aatggcaciaa tggattcaaa tgggacattt gttaatgtaa caatgagcac atttaactgg 480
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<210> 79

<211> 497

<212> DNA

<213> Homo sapiens

<400> 79

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 aggtcacttt tatgttttgg atgggcaaaa agacccttta ctctgtggaa atgggttcaga 180
 tgcagggtaa gaaacataat atatattttt aagatataga actctttgcg aaaaaaaaaa 240
 gtaggtagga aaacaactac atgggttatat gtgtagcctt accatgtatg caataaagag 300
 cagtgtctgt cccctaggaa gtgccttgtc tgccttaccg gattgccact ggtcctaaac 360
 tcacagcaat taaaaattat ccctttgtga agacctttcc ccaaaatttc acagttaaga 420
 tgttcttaaa ttgatgtctc aatgtgtgaa ggcccagagt ctgtctttgc tgtacatcta 480
 tcagagctgt taggaaa 497

<210> 80

<211> 501

<212> DNA

<213> Homo sapiens

<400> 80

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 tcatctgata agtttcacgg tgggcaatca cctaaagtgt tctggaaatt aaagcaagat 180
 aattcgtcac agatagcagc tttgggtttt gaaaattcct ataagtcaaa taaattgaaa 240
 ttgctgtaat ttctaaactg accctacctc catttctctc tcttatagcc agtgtccaga 300
 aggatacatc tgtgtgaagg ctggtcgaaa cccaactat ggctacacaa gctttgacac 360
 cttagctgg gctttcctgt ctctatttcg actcatgact caagactact gggaaaatct 420
 ttaccagttg gtaagggtcca aatgagcatg cataacattt atttttatag acatgtatga 480
 aatgaaaagc ataggctgag t 501

<210> 81

<211> 432

<212> DNA

<213> Homo sapiens

<400> 81

agctaattag tctactgact atctaactgt ggtaatcaga tattttatttg gggacattat 60

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actaaaatac tgatggaatt atccccatt tcccctagac attacgtgct gctgggaaaa 120..
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tcctggctgt ggtggccatg gcctatgagg ggcagaatca ggccaccttg gaagaagcag 240
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ctcagggtact gagtataaaa mgcaaagatt tatcattatt attmtagtt tctaagtaga 360
aatagtgtta tactatagag ggtagattgg aactgctttt tcattttata tatmggcatt 420
gtcattagac ac 432

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<210> 82

<211> 489

<212> DNA

<213> Homo sapiens

<400> 82

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gttggaagt tcttcagaag catcaaagtt gagttccaaa agtgctaaag aatggaggaa 180
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tactaagtgc tctggtttct ttgtcattgc tattgctttt tagtttttgt attttgtttt 420
ggtacacttt tgtactatct gtacttcagt tgagggacag ggaactaaca tttaatatag 480
ttgtttaa 489

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<210> 83

<211> 653

<212> DNA

<213> Homo sapiens

<400> 83

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gtgaagacta aatgaagtgg ttgtatactt agtaaattgc aaatcagtat tgtagtcag 60
aaaaacactc tttgtactta aatttgcttt aataaaaaata tcaaatata tgtgtcctct 120
ataaatttga ttatccatgt ttaagggaag gagtatacta actccaaaga aaacagatcc 180
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ctttttgctt tctctgcagt ctctcttgag tatccgtggc tcctgtttt cccaagacg 300
caatagcaaa acaagcattt tcagtttcag aggtcgggca aaggatgttg gatctgaaaa 360
tgactttgct gatgatgaac acagcacatt tgaagacagc gaaagcagga gagactcact 420
gtttgtgccg cacagacatg gagagcgacg caacagtaac gttagtcagg ccagtatgtc 480
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atggtgtggt ttcccttggtg ggtggacctt cagctctaac gtcacctact gggcaacttc 600
cccagaggtg ataatatagat acctagctgc tactgacatt attcaccaat ttg 653

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<210> 84

<211> 566

<212> DNA

<213> Homo sapiens

<400> 84

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gaattctctt aaaggtacta cctgtgatac tttttttaa aaaaaactgt ttataactta 60
gcaataattc aatattttat tcttgaaatt cttacctgga aaattgcatg tagcatgatt 120
tgcaagaaa tgctatgtgg tgttgattta cttattggga agagtgggtt gagccatcag 180
tatttggttt gcagggcacc accactgaaa cggaagtcag aaagagaagg ttaagctctt 240
accagatttc aatggagatg ctggaggatt cctctggaag gcaaagagcc gtgagcatag 300
ccagcattct gaccaacaca atggaaggta agagcaggtc atggaacagc caactttctg 360
tgattatgtg ctttgtgaac tattccttct tttcatagaa ttactgaagt ctgttaccct 420
gatcgaacta tatattagac ctaagaatgt gatatatggt gtacattatc acattgntta 480
caaaactaat attggcctta ttctttttga cttgggtcct taccttactt gcagagtgat 540
atttcaacac ttgatattat atcaat 566
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<210> 85

<211> 748

<212> DNA

<213> Homo sapiens

<400> 85

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aaaaagtcga tctatatgac attttaatta acattttctg aaaatattta atgggattgt 120
cttctcaagt ttcttaagta atatgaactt ctattttcaa atataagcat caattttgtt 180
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gatttgccaa tgtgttcttg atctgggact gctgtgatgc atggttaaaa gtaaaacatc 360
ttgtgaattt aattgttatg gatccatttg ttgatcttgc catcactatt tgcatgtgtc 420
taaataccct ctttatggcc atggagcact accccatgac tgagcaattc agtagtgtgt 480
tgactgtagg aaacctggta agtacatttg aagtttactt atttactttg gtagatgtgg 540
gagagataga ccaaagggaa agatgtattt gtgctgtgtt gaacccaaaa attatatacct 600
ctttcctcat agaaagaaat atctaaggaa tattacaggg aatctcagag atacagccta 660
aaactcaact ggtatgaatg ctgattgttt aggccaatgt ctgtgctgat tgatcatggt 720
gtcttaccag ttgtaaacgt ctcaaat 748
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<210> 86

<211> 664

<212> DNA

<213> Homo sapiens

<400> 86

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agtgtgtatc tctaattttt taggtcttta ctgggatttt tacagcagaa atgggttctca 180
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tgcgatcatt cagactggta tctatttata tatatccctg tcgctcattg gcacaacatt 360
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tattttgaaa ttgaatcaat gtatatattat ataattatta attttaattt taaattttaca 420
 tcaatatgtg acatttctaag aaaacatgta aacatccyct ttaaagctaa accatttttct 480
 aagaatgatg aaagcattca aaatactcta taatgattag gtatgtaggg cacattagaa 540
 aacctacaag tacttttctaa aactgtgttt taagtttatg aagctttttt ggccttacag 600
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 tact 664

<210> 87

<211> 750

<212> DNA

<213> Homo sapiens

<400> 87

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 ccacgtgtgg ttctatgata ccacatacta ataaaataat gtctaaaatt atattatgat 180
 tactactaac agcatctttt cacttgatta cagcttagag ttttcaagtt ggcaaatcc 240
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 aacttctcct gggctctggt ttccatttt 750

<210> 88

<211> 768

<212> DNA

<213> Homo sapiens

<400> 88

ccttagagca ggatattagg tccttttaaag agtgtgtgac ttagacatgg catctgaaat 60
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 ttttaggctg ttattttaaat gcatatttca atattaarat aggcattttt ctttttttct 180
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 ctgctactga tgaatgacaat gaaatgaata atctgcagat tgcagtagga agaattgcaa 300
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 ggaatgcttt taaatttttt gttccatttc ctatgataac catgtactac agttatttac 720
 tattttcatt gtgcttatat gcattatcga aaagcaatga ttgtaagt 768

<210> 89
 <211> 471
 <212> DNA
 <213> Homo sapiens

<400> 89
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 ttgaaatggg attttgtttc cagaaattaa atgcaaccag ctcatctgaa ggaagcacag 180
 ttgatgttgt tctaccccga gaaggatgaac aagctgaaac tgaacccgaa gaagaccta 240
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<210> 90
 <211> 623
 <212> DNA
 <213> Homo sapiens

<400> 90
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 tttgcagaga cattctgtaa oca 623

<210> 91
 <211> 520
 <212> DNA
 <213> Homo sapiens

<400> 91
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 ccatttaagt aaaataaaat atttttgatt cataggcctt tgaagatata tacattgaac 180
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 ttctggaaat gcttctcaaa tgggttgctt atggatttca aacatatttc actaatgcct 300

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ggtgctggct agatttcttg atcgttgatg taagtatttt aagtgatttt tataaaattg 360
tttttaaaag aggcaagttt gacatttcat atgtttctgt tattaaaact ttcactaata 420
atgacataat tatgcagtta tttaaacaaa actgtaacat atgcaacaat gaggaatata 480
tcatgggaaa gagtagagga ggtcctaaac atgggcagtg 520

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<210> 92

<211> 595

<212> DNA

<213> Homo sapiens

<400> 92

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atcagtggta tatgcacaag ttgaaaagg gtccatggta taaaatatct aactggagat 120
attgacacgt gttgataaat atgggcaagt attctggttt cattgggttaa aaaaaagcaa 180
tagtatgaga tgagactggc aatataagat gacccacta tgtggaagat gaaagttgcc 240
aaggatatgtc caaattagta tttagtctgc attaaataga taccacaccc tataccttca 300
gtcaacagtt tatttcttgg tgaactaatt aattttttt tccttttgta ggtttctttg 360
gttagcctgg tagccaatgc tcttggttac tcagaactcg gtgccatcaa atcattacgg 420
acattaagag cttaagacc tctaagagcc ttatcccggt ttgaaggcat gagggtaaga 480
agaatagaça ctctaattat tcatgtcaaa aattacatgt aggtaatgat ttagatagaa 540
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<210> 93

<211> 787

<212> DNA

<213> Homo sapiens

<400> 93

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catactgtag catattttgc tttccttaaa accttagctc tttagttgtg tcattgtttg 120
ttttccttca aatatgtgct agaaaaatta gaagaaacaa cttgtccacc tagattttta 180
tttaactctt ttcaagcaca tattaatact aaacaaatac attgaaggaa tggtttccat 240
tcaaaagggt tgtaagctat gttcccctcg ctgtctcttc taggtgggtg tgaatgctct 300
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ctttagcatc atgggtgtga atttgtttgc tggcaagttc taccactgtg ttaacatgac 420
aacgggtaac atgtttgaca ttagtgatgt taacaatttg agtgactgtc aggctcttgg 480
caagcaagct cggtggaata acgtgaaagt aaactttgat aatgttggcg ctggctatct 540
tgactgctt caagtggtaa gtggctactg tacgagtttt gaaaaagttt tcaagatggt 600
tcaaggaaga ttatttccct gatgttcttc gtttgaatga ctaacatttg acagcatgaa 660
aaaaagttta tgataacacc tataatatca gcttgaattg atcataaaaa agatgttaca 720
attattttat aatgtatttt ccttagtggt aagcttttag tatgttttaa tgtgatttta 780
tatttct 787

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<210> 94

<211> 438

<212> DNA

<213> Homo sapiens

<400> 94

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ctcttgatat gaaatttcac aatattgtac aaaaagttat ttgttataat actgtcagat 120
tttcatctgg ttaaagtgtca ttgttaggtg aaatttttat gaacaattca aatatatgtt 180
atttacaggc cacatttaaa ggctggatgg atattatgta tgcagctgtt gattcacgag 240
atgtaagtat cactcaaata ttatttatag gttctagatt tcttatgggtg aatattgggtg 300
gtaatttaaa cactgatata tccaaaattc tatattagaa catttaatat tgcataataa 360
aatgaacag tctgcttcaa tatagatgat gcttgattaa tgtgtgccta atatacaata 420
tgtagcta atgaaacg                                     438

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<210> 95

<211> 637

<212> DNA

<213> Homo sapiens

<400> 95

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gtaaggcaca atgggaaaag agaatcaaga acaatcataa aacttgcaaa ccttcatttt 60
actagatcat actagtttta aaaaattgtt tttgtagaac aatatctcag ggtaaggcaa 120
aagtagcact gtattaagta acagcactca ataaattact gatttagtgt aagtatttat 180
agtatttttc atattattta atattttcaa tatcatttag gttaaacttc agcctgtata 240
tgaagaaaat ctgtacatgt atttataact tgtcatcttt atcatctttg ggtcattctt 300
cactctgaat ctattcattg gtgtcatcat agataacttc aaccagcaga aaaagaagat 360
aagtattctt tagcttttac ctttcttcat tctgggggttc tgtctgttaa tacagccaaa 420
taaccagaat acctgtgggc atgacagact taaatcatgt ttatattatt ttcagttgcc 480
catgtgggta ttaagctgc agggattcca gcctctagtc agtggctcct ctcaaagttt 540
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<210> 96

<211> 637

<212> DNA

<213> Homo sapiens

<400> 96

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tttatgtacg taaggatttt gcataatatt aagatattca gaatttcaca taaatgggaa 120
aagcaggata aatgtatatg taggaggata atatccactt aaaaattaga aaagattaaa 180
ggaaagacaa atattttttg tgaaagtact attggaacac agaattgtaa ccagttttat 240
actatgtctt tactttggag gtcaagacat ctttatgaca gaggaacaga aaaaatatta 300
caatgcaatg aagaaacttg gatccaagaa acctcagaaa ccatacctc gccagcagt 360
aagaattact tgtctccttt aatgttccaa agccatgcgt ccatatggtc aaattgagca 420
atgctctgga gcagaacata ttaggtgata tcaccaatat tgagccctaa ttataaagtt 480
catattttgc atcataattc acaacttctg cactcattag gagttaccac attccaaaaa 540

```

aaggaggtaa tgttctttat aatttgtgag ttgaaaactt ctagctcagg gttcctaata 600.
aatacttcca aagcaaggtt cactttcctg ctaccaa 637

<210> 97

<211> 759

<212> DNA

<213> Homo sapiens

<400> 97

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gaagagaaaa aaagcacaca aaattgtttg gggaatatg aggaggggtgc acatccatcc 120
cgtatgtgga agggctttat ctacaatttt actgcattat tctttatgaa atatatatag 180
taaccttatt tctcttctct cactttctag aacaaattcc aaggaatggt ctttgatttt 240
gtaaccagac aagtctttga tatcagcatc atgacctca tctgcctcaa catggtcacc 300
atgatgggtg aaacggatga ccagggcaaa tacatgaccc tagttttgtc ccggatcaac 360
ctagtgttca ttgttctgtt cactggagaa tttgtgctga agctcgtctc cctcagacac 420
tactacttca ctataggctg gaacatcttt gactttgttg tggtgattct ctccattgta 480
ggtaagaaca gcttaattac caagaggat agttacagag aaacagttgc cccaggacct 540
tctagctgat taacatggaa attaggtctg agaataataa tgcatataga tgtaaagttc 600
aacactagca tttttgaata aaaactctga aacctgggtt tattcacaaa gctaactagt 660
tagaaacat gtttaggaata ccagatttg gaaagagggtg aagaagacag gaaataaaca 720
ttatcaggta ctctcctaatt cttaaaccac ggtcacagg 759

<210> 98

<211> 3975

<212> DNA

<213> Homo sapiens

<400> 98

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caagtttggt gtgttcatag accttaaaaa agataaagcc atcatgtaaa gtgaaaagat 120
attatctgtt tagctgtgtt ctatgttttc cataggatg tttctggctg agatgataga 180
aaagtatttt gtgtcccta ccttggtccg agtgatccgt cttgccagga ttggccgaat 240
cctacgtctg atcaaaggag caaaggggat ccgcacgctg ctctttgctt tgatgatgtc 300
ccttctgctg ttgtttaaca tcggcctcct gctcttctg gtcattgtta tctatgccat 360
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ctttgagacc tttggcaaca gcatgatctg cttgttccaa attacaacct ctgctggatg 480
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gatgttctat gaggtttggg aaaagtttga tcccgatgcg acccagttta tagagttctc 780
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<210> 99

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 99

tgtgttctgc cccagtgaga ct

22

<210> 100

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 100

cttcctgctc tgcccaaact gaat

24

<210> 101

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 101

ggcgatgtaa tgtaaggtgc tgtc

24

<210> 102

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 102

gtgccttcag ttgcaattgt tcag

24

<210> 103

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 103

ttaggaattt catatgcaga ataa

24

<210> 104

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 104

tgggccattt ttcgtcgtc

19

<210> 105

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 105

gaaagacgca ttgcagaaga aaagg

25

<210> 106

<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 106
ctattggcat gtgttggtgc taca

24

<210> 107
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 107
gtgctgggtt ctcatttaac ttac

25

<210> 108
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 108
ttcccaactt aatttgatat ttagc

25

<210> 109
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 109

gcagtttggg cttttcaatg ttag

24

<210> 110

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 110

gacacagttt caraatcccr aatg

24

<210> 111

<211> 24

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 111

ttagggctac gtttcatttg tatg

24

<210> 112

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 112

agcactgatg gaaaaccaa ctat

24

<210> 113

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 113

agcccatgca gtaatataaa tcct

24

<210> 114

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 114

tccaggctga taagctatgt ctaa

24

<210> 115

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 115

ctgtggcctg cctgagcgta tt

22

<210> 116

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 116

ccaattctac tttttaagga aatg

24

<210> 117

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 117

aaatacttgt gcctttgaa

19

<210> 118

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 118

gtacatacaa tatacacaga tgc

23

<210> 119

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 119

aggcagcaga acgacttgta ata

23

<210> 120

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 120

atccggtttt aatttcataa ctca

24

<210> 121
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 121
gttgagcacc cttagtgaat aata 24

<210> 122
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 122
tcacacgctc tagactactt ctct 24

<210> 123
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 123
tgcaaatact tcagcccttt caaa 24

<210> 124
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 124

ttccccacca gactgctctt tc

22

<210> 125

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 125

gcagcaggca ggctctca

18

<210> 126

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 126

tctcccatgt ttttaattttc aacc

24

<210> 127

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 127

ataatcttgc aaaatgaaat caca

24

<210> 128

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 128

atccgggatg acctactgg

19

<210> 129

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 129

gataacgaga gccgtagaga ttcc

24

<210> 130

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 130

agccagccat gcctgaacta

20

<210> 131

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 131

tgtttgcttg tcatattgct caa

23

<210> 132
<211> 22
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 132
tgcactattc ccaactcaca aa

22

<210> 133
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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 133
aagggtgtct ctgtaacaaa aatg

24

<210> 134
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 134
gtgatggcca ggtcaacaaa

20

<210> 135
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 135
ctgggactgt tctccatatt gggt

24

<210> 136
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 136
tttgcagggg ccaggaag

18

<210> 137
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oligonucleotide

<400> 137
cattgtggga aaatagcata agc

23

<210> 138
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 138
gcaagaaccc tgaatgtag aaa

23

<210> 139
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 139

taatgctttt aagaatcata caaa

24

<210> 140

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 140

ccagcgtggg agttgacaat c

21

<210> 141

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 141

cggcatgcag ctctttgta

20

<210> 142

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 142

atgtgccatg ctggtgtatt tc

22

<210> 143
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 143
cacccatctt ctaatcacta tgc

23

<210> 144
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 144
cagcaatttg gagattattc att

23

<210> 145
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 145
gcagccactg atgatgataa

20

<210> 146
<211> 21
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 146
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<210> 148
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gtattcatatc ctaccacac ctat 24

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<210> 150
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24

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ggctgaatgt ttccacaact

20

<210> 152

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21

<210> 153

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aggcagagga aaacaatgg

19

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23

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21

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21

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20

<210> 158

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18

<210> 159

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24

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23

<210> 161

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23

<210> 162

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23

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24

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21

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24

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22

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21

<210> 168

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19

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24

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23

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24

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cttgttttcg ttttaaagta gta

23

<210> 173

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caaagatcac cctggaagct cagtt

25

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25

<210> 175

<211> 23

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23

<210> 176

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21

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24

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22

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<400> 179

tgagaaatag gctaaggacc tcta

24

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<400> 180
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17

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<400> 181
aaggggtgca aacctgtgat ttt

23

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oligonucleotide

<400> 182
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21

<210> 183
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<400> 183

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24

<210> 184

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tctttattag ttttgacat tttta

24

<210> 185

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caatccttcc aaggtctcct atc

23

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tttcatcttt gccttcttgc tcat

24

<210> 187

<211> 22

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22

<210> 188

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tcccctttac acagagtcac agtt

24

<210> 189

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<213> Homo sapiens

<400> 189

gcatttgaag atata

15

<210> 190

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<212> DNA

<213> Homo sapiens

<400> 190

gcatttgacg atata

15

<210> 191

<211> 15

<212> DNA

<213> Homo sapiens

<400> 191

atcatatcct tcctg

15

<210> 192
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<400> 192
atcatatmct tcctg

15

<210> 193
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24

<210> 194
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oligonucleotide

<400> 194
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24

<210> 195
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<400> 195
acaggaaatg cctcttctta cttc

24

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oligonucleotide

<400> 196
tttccccaag gattctacta ctgt

24

<210> 197
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oligonucleotide

<400> 197
agtgcattgta actgacacaa tcac

24

<210> 198
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oligonucleotide

<400> 198
cttgcggtcc tgtttggtc tct

23

<210> 199
<211> 22
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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 199

tccgcttctt taccaggga tc

22

<210> 200

<211> 24

<212> DNA

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<400> 200

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24

<210> 201

<211> 24

<212> DNA

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<223> Description of Artificial Sequence: synthetic
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<400> 201

cagggcaata ttataaata atgg

24

<210> 202

<211> 24

<212> DNA

<213> Artificial Sequence

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<400> 202

tttgaaaat gtgtagctca ataa

24

<210> 203

<211> 22

<212> DNA

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oligonucleotide

<400> 203

aaggcatggt agtgcataaa ag

22

<210> 204

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<212> DNA

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<400> 204

atgaaacata aagggaggtc aa

22

<210> 205

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<400> 205

aatgtgagct tggctattgt ctct

24

<210> 206

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<212> DNA

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oligonucleotide

<400> 206

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23

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oligonucleotide

<400> 207
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22

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oligonucleotide

<400> 208
caacaaggct tctgcacaaa ag

22

<210> 209
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<400> 209
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19

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20

<210> 211
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20

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20

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<400> 213
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22

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<400> 214

tatcccttgctctttcattt atct

24

<210> 215

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<400> 215

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24

<210> 216

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24

<210> 217

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oligonucleotide

<400> 217

gcgtgtttgc gctaataag

18

<210> 218

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<400> 218

ctaagtcact tgattcacat ctaa

24

<210> 219

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acagggtggc tgaagtgttt ta

22

<210> 220

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oligonucleotide

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20

<210> 221

<211> 23

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<400> 221

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23.

<210> 222

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<400> 222

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24

<210> 223

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<223> Description of Artificial Sequence: synthetic
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<400> 223

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24

<210> 224

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<212> DNA

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24

<210> 225

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oligonucleotide

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24

<210> 226

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24

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<400> 227

ggtgctggtg ggataggagt tttt

24

<210> 228

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oligonucleotide

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24

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oligonucleotide

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tcagaggggt gctttcttcc acat

24

<210> 230

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24

<210> 231

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oligonucleotide

<400> 231

gcaaaggaca ttggctctga gaat

24

<210> 232

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oligonucleotide

<400> 232

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23

<210> 233
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oligonucleotide

<400> 233
tgggctttgc tgctttcaa

19

<210> 234
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oligonucleotide

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24

<210> 235
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oligonucleotide

<400> 235
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21

<210> 236
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oligonucleotide

<400> 236

gtgatggcca ggtcaacaaa

20

<210> 237

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oligonucleotide

<400> 237

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23

<210> 238

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oligonucleotide

<400> 238

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24

<210> 239

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24

<210> 240

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oligonucleotide

<400> 240

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24

<210> 241

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oligonucleotide

<400> 241

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23

<210> 242

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oligonucleotide

<400> 242

gtgccagcgt gggagttc

18

<210> 243

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oligonucleotide

<400> 243

gtgggggctc taggaaacct

20

<210> 244

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oligonucleotide

<400> 244

tttaatgaaa atgaggaaaa tggt

24

<210> 245

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oligonucleotide

<400> 245

gaccaagcat ttttatttca ttc

23

<210> 246

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oligonucleotide

<400> 246

agtggcagca agattgtca

19

<210> 247

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oligonucleotide

<400> 247

ggccttgctt ttgagttcc

19

<210> 248

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oligonucleotide

<400> 248

ggtctttgcc tatttctatg gtg

23

<210> 249

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oligonucleotide

<400> 249

ttaaaccgct tgaagatcta aata

24

<210> 250

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oligonucleotide

<400> 250

tatacaccaa aatatctcct tat

23

<210> 251

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oligonucleotide

<400> 251

ggggcacacc taattaattt ttat

24

<210> 252

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oligonucleotide

<400> 252

aaaggagata ctcaagacca cata

24

<210> 253

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<223> Description of Artificial Sequence: synthetic
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<400> 253

cccaccaaca caaatatacc taat

24

<210> 254

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oligonucleotide

<400> 254

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22

<210> 255
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oligonucleotide

<400> 255
tccagcctta ggcacctgat aa

22

<210> 256
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oligonucleotide

<400> 256
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24

<210> 257
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oligonucleotide

<400> 257
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24

<210> 258
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oligonucleotide

<400> 258
tgacatttcc atggtacaaa gtgt

24

<210> 259
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oligonucleotide

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23

<210> 260
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oligonucleotide

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ccacctggca gtttgattg

19

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25

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20

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22

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26

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20

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22

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23

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24

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24

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24

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21

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22

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9

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20

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24

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22

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21

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24

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24

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23

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21

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20

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24

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20

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24

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24

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24

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22

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oligonucleotide

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agagcacctt gaaggaaaca acaa

24

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24

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23

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19

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20

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22

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24

<210> 351

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oligonucleotide

<400> 351

gatggcaaga tcaacaaatg ga

22

<210> 352
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23

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oligonucleotide

<400> 353
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23

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oligonucleotide

<400> 354
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24

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oligonucleotide

<400> 355

gtgccaatga gcgacagg

18

<210> 356

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<400> 356

ccacgtgtgg ttctatgata cc

22

<210> 357

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accgtgggag cgtacagtca

20

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cggcatgcag ctctttgta

20

<210> 359

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tgccacggt cctagctact gtc

23

<210> 360

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gagttccctt tttaggctgt tatt

24

<210> 361

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tcttattgcc ttcattgatt tcta

24

<210> 362

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tgaaaaataa gatgcgggag tg

22

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oligonucleotide

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21

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oligonucleotide

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gagatgggaa tggaaccacc a

21

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oligonucleotide

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23

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oligonucleotide

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21

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24

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19

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24

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ttcttttgta ctcactatta tactaa

26

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aaacttgcct cttttaaaaa caat

24

<210> 372

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taccacaccc tataccttca gtca

24

<210> 373

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oligonucleotide

<400> 373

gagtatggca cccttttcta tcta

24

<210> 374

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oligonucleotide

<400> 374
gctatgttcc cctcgctgtc t

21

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oligonucleotide

<400> 375
tgcttgccaa gagcctgac

19

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oligonucleotide

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22

<210> 377
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<220>
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oligonucleotide

<400> 377

caaacgaaga acatcaggga aata

24

<210> 378

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<213> Artificial Sequence

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oligonucleotide

<400> 378

ttcacatat tgtacaaaaa gtta

24

<210> 379

<211> 24

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<400> 379

attaccacca atattcacca taag

24

<210> 380

<211> 23

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tcagggtaag gcaaaagtag cac

23

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gaaccccaga atgaagaaag gtaa

24

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acgcatggct ttggaacat

19

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aacggatgac cagggcaaat ac

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24

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23

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<400> 400
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18

<210> 401
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<213> Homo sapiens

<400> 401
caagatgatg atgag

15

<210> 402
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<212> DNA
<213> Homo sapiens

<400> 402
tggtgtaagg tag

13

<210> 403
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<400> 403
tggtataagg tag

13

<210> 404
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<213> Homo sapiens

<400> 404
ccccttatat ctccaac

17

<210> 405
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<213> Homo sapiens

<400> 405

ccccttatay ctccaac

17

<210> 406

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<213> Homo sapiens

<400> 406

aaatacgtaa tcgat

15

<210> 407

<211> 15

<212> DNA

<213> Homo sapiens

<400> 407

aaatacataa tcgat

15

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<213> Homo sapiens

<400> 408

aaatacrtaa tcgat

15